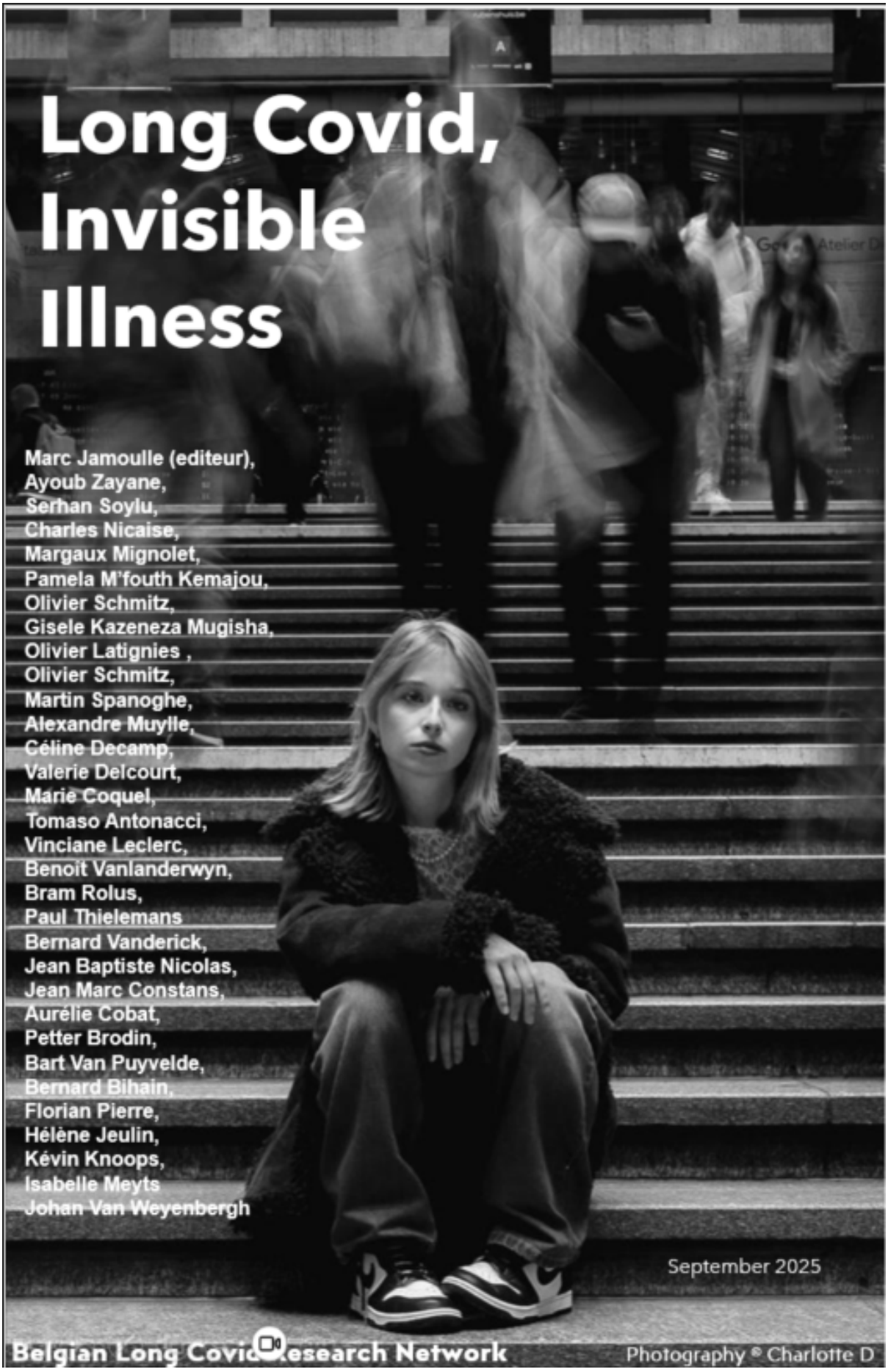

Long Covid, Invisible Illness

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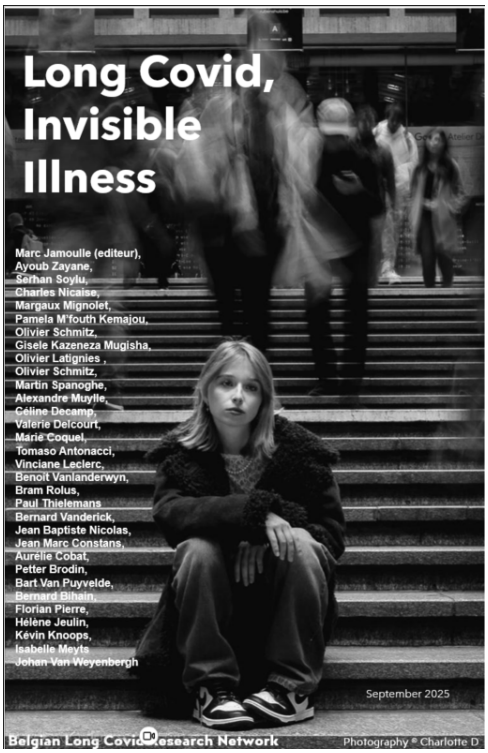
September 2025

Belgian Long Covid Research Network

Photography © Charlotte D

Long COVID, invisible illness

Belgian Long COVID Research Network



Cover photograph by Charlotte Detinne,
in testimony to the Long COVID that undermines it.

September 2025

Marc Jamoulle (ed.)

« What we cannot name, we cannot think. »
Michel Foucault – *Les mots et les choses* (1966)

« I am invisible, understand, simply because people refuse to see me. »
Ralph Ellison – *Invisible Man* (1952)

Foreword

It is an honour and a privilege to write this brief introductory note to this research reporte entitled: "Long COVID, the invisible illness scrutinised by the Long COVID Belgium Research Network". The report, written by Marc Jamoulle and the members of the Network, is timely and of great importance.

"Long COVID" is a pathological condition in search of a solution, and the surest path toward a therapeutic resolution lies in a deep understanding of its pathogenesis. Likewise, nothing better elucidates the cause and mechanism of a mysterious disorder than a multidisciplinary, patient-centred approach bringing together expert clinicians and scientists. This kind of collaboration builds a bridge between the patient's bedside and the laboratory, and it goes without saying that traffic on this bridge must flow in both directions.

As of May 2025, the pathogenesis of Long COVID remains unclear. Nevertheless, that of hypoxaemic COVID pneumonia, the multisystem inflammatory syndrome in children, "COVID toes", and neuro-COVID has already been elucidated — at least in some patients. This is most encouraging and attests to the validity of the multidisciplinary approach. There is therefore no reason to doubt that a major breakthrough for Long COVID is within reach.

There is no doubt that the brilliant efforts undertaken by the members of the Long COVID Belgium Network will play a key role in the study of Long COVID. This initiative will benefit patients worldwide and deserves to be enthusiastically supported and encouraged, without any reservation.

Professor Jean-Laurent Casanova
The Rockefeller University & Hôpital Necker-Enfants Malades

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Keywords
Long COVID; **Post-Acute COVID-19 Syndrome**; **Chronic Fatigue Syndrome**; **Human Phenotype Ontology**; **Neuroimaging**; **Neurobiology**; **Multiomics**; **Family Practice**; **Primary Health Care**; **Patient-Centered Care**; **Patient partnership**; **Rehabilitation**; **Quality of Healthcare**; **Surveys and Questionnaires**; **COVID-19**; **DUSOI**; **COOP WONCA-Charts**.

Executive Summary

Design and Multidisciplinary Framework

This self-initiated, independently funded research program, originating in general and family practice, adopts a multidisciplinary framework by engaging patients as active partners throughout the research process. The approach integrates diverse methodologies, including:

— **Narrative medicine**: systematic listening and structured symptom analysis using the Human Phenotype Ontology.

— **Multi-omics**: whole genome/exome sequencing, transcriptomics (global and targeted), plasma proteomics (quantitative and untargeted), and lipidomics.

— **Systemic immunology**: high-parameter flow cytometry, multiplex serum assays, and single-cell RNA sequencing.

— **Neurobiology**: investigation of patient-derived autoantibodies and their role in pain symptomatology via in vivo and in vitro modeling.

— **Functional neuroimaging**: Tc-99m HMPAO brain perfusion SPECT-CT and single-voxel MR spectroscopy (MRS) to detect metabolic changes invisible to conventional MRI.

— **Molecular virology and structural biology**: characterization of SARS-CoV-2 and host interactions at molecular and structural levels.

— **Anthropological inquiry**: longitudinal interviews exploring illness narratives, healthcare navigation, and social legitimacy.

— **Epistemological analysis**: reflection on co-production of new disease categories by molecular data, clinical practice, and patient expertise within quaternary prevention ethics.

— **Computer science and biostatistics**: integration and analysis of clinical, paraclinical, and multi-omics datasets.

— **Patient partnership**: collaboration with patients and the Long COVID Belgium association to guide research priorities and interpretation.

— **Social partnership**: engagement with community organizations, including *Le Ressort* in Gembloux, to address social dimensions of illness and care.

Anthropological and Epistemological Contributions

— Qualitative investigations highlight diagnostic contestation, identity disruption, and disparities in access to care, informing research priorities and patient-centered outcome measures.

— Epistemological analysis underscores the tension between rapid molecular advances and slower clinical adaptation, stressing the ethical imperative to prevent both over- and underdiagnosis within quaternary prevention.

Methodological Innovations

— Use of large language models (LLMs) to analyze patient narratives and classify symptoms within standardized ontologies (e.g., Human Phenotype Ontology), introducing the concept of a *terminological biomarker*.

— Cross-disciplinary collaboration among general practitioners, specialists, multi-omics researchers, immunologists, neurobiologists, epidemiologists, anthropologists, and computer scientists.

— Systematic patient involvement through symptom diaries, clinical interviews, the Long COVID Belgium association, and contributions from *Le Ressort* social workers.

Main Recommendations

1. **Official recognition** of Long COVID as a chronic and disabling condition requiring sustained medical, social, and policy attention.
2. **Interdisciplinary expertise centers** integrated with primary care to improve diagnosis, management, and research coordination.
3. **Standardization of clinical data** through structured ontologies (HPO) and harmonized data models (OMOP).
4. **Political and financial mobilization** to support research, train healthcare professionals, and ensure dignified patient care.
5. **Reduction of healthcare access inequalities** by addressing socio-economic and educational disparities across cohorts.

Conclusion

By integrating high-resolution biology and advanced imaging within a reflexive social science framework, the Belgian Long COVID Research Network has advanced the field from anecdotal reports of recurrent symptoms to coherent, multimodal evidence of SARS-CoV-2 persistence. This multidisciplinary approach provides a robust foundation for precision diagnostics, targeted therapies, and ethically grounded clinical practice for Long COVID and other post-infectious syndromes. It underscores the central role of general practice in early identification and management of emerging pathologies and calls for a paradigm shift in research, healthcare delivery, and governance addressing invisible chronic diseases.

Resumen Ejecutivo

Diseño y Marco Multidisciplinario

Este programa de investigación, auto-iniciado y financiado de manera independiente, originado en la medicina general y familiar, adopta un marco multidisciplinario al involucrar a los pacientes como socios activos a lo largo de todo el proceso de investigación. El enfoque integra diversas metodologías, incluyendo:

- **Medicina narrativa**: escucha sistemática y análisis estructurado de los síntomas utilizando la Ontología del Fenotipo Humano (HPO).
- **Multi-ómica**: secuenciación del genoma/exoma completo, transcriptómica (global y dirigida), proteómica plasmática (cuantitativa y no dirigida) y lipidómica.
- **Inmunología sistémica**: citometría de flujo de alta complejidad, ensayos séricos multiplex y secuenciación de ARN de célula única.
- **Neurobiología**: investigación de autoanticuerpos derivados de pacientes y su papel en la sintomatología del dolor mediante modelos in vivo e in vitro.
- **Neuroimagen funcional**: SPECT-CT de perfusión cerebral con Tc-99m HMPAO y espectroscopía de RM de vóxel único (MRS) para detectar alteraciones metabólicas invisibles a la RM convencional.
- **Virología molecular y biología estructural**: caracterización detallada del SARS-CoV-2 y sus interacciones con el huésped a nivel molecular y estructural.
- **Investigación antropológica**: entrevistas longitudinales que exploran narrativas de enfermedad, navegación del sistema de salud y construcción social de la legitimidad.
- **Análisis epistemológico**: reflexión crítica sobre la co-producción de nuevas categorías de enfermedad por datos moleculares, práctica clínica y experiencia del paciente, dentro del marco ético de la prevención cuaternaria.
- **Informática y bioestadística**: integración y análisis de datos clínicos, paraclínicos y multi-ómicos.
- **Alianza con pacientes**: colaboración con pacientes y la asociación Long COVID Bélgica para guiar prioridades de investigación e interpretación.
- **Alianza social**: colaboración con organizaciones comunitarias, incluyendo la asociación sin fines de lucro *Le Ressort* en Gembloux, para abordar las dimensiones sociales de la enfermedad y la atención.

Contribuciones Antropológicas y Epistemológicas

- Las investigaciones cualitativas destacan la contestación diagnóstica, la disrupción de la identidad y las disparidades en el acceso a la atención, informando las prioridades de investigación y las medidas de resultado centradas en el paciente.

— El análisis epistemológico subraya la tensión entre los rápidos avances moleculares y la lenta adaptación clínica, enfatizando la responsabilidad ética de evitar tanto el sobre-diagnóstico como el sub-diagnóstico dentro del marco de la prevención cuaternaria.

Innovaciones Metodológicas

— Uso de modelos de lenguaje de gran escala (LLMs) para analizar narrativas de pacientes y clasificar síntomas dentro de ontologías estandarizadas (p. ej., Ontología del Fenotipo Humano), introduciendo el concepto de un *biomarcador terminológico*.

— Colaboración interdisciplinaria entre médicos generales, especialistas, investigadores en multi-ómica, inmunólogos, neurobiólogos, epidemiólogos, antropólogos e informáticos.

— Participación sistemática de pacientes mediante diarios de síntomas, entrevistas clínicas, la asociación Long COVID Bélgica y contribuciones de los trabajadores sociales de *Le Ressort*.

Recomendaciones Principales

1. **Reconocimiento oficial** del Long COVID como una condición crónica y discapacitante que requiere atención médica, social y política sostenida.
2. **Centros de experiencia interdisciplinaria** integrados con la atención primaria para mejorar el diagnóstico, el manejo y la coordinación de la investigación.
3. **Estandarización de datos clínicos** mediante ontologías estructuradas (HPO) y modelos de datos armonizados (OMOP).
4. **Movilización política y financiera** para apoyar la investigación, capacitar a los profesionales de la salud y garantizar una atención digna a los pacientes.
5. **Reducción de las desigualdades en el acceso a la atención** abordando las disparidades socioeconómicas y educativas entre las cohortes.

Conclusión

Al integrar biología de alta resolución e imagen avanzada dentro de un marco reflexivo de ciencias sociales, la Red Belga de Investigación sobre Long COVID ha hecho avanzar el campo desde informes anecdóticos de síntomas recurrentes hacia evidencia multimodal coherente de la persistencia del SARS-CoV-2. Este enfoque multidisciplinario proporciona una base sólida para el desarrollo de diagnósticos de precisión, terapias específicas y una práctica clínica éticamente fundamentada para el Long COVID y otros síndromes post-infecciosos. Además, subraya el papel central de la medicina general en la identificación temprana y el manejo de patologías emergentes, y llama a un cambio de paradigma en la investigación, la atención sanitaria y la gobernanza de las enfermedades crónicas invisibles.

Chapter 1

Introduction

By Marc Jamoulle

1.1 Objectives of the Report

This report aims to provide an overview of the current state of knowledge about the disease that patients have named Long COVID—soon to be recognized as chronic COVID. We describe the organization and missions of the Long COVID Belgium Research Network and explain how clinical data collected in general practice are used in collaboration with laboratories and research centers, in full partnership with patients and their associations.

Approaching a new disease begins with the careful observation of facts. Since paraclinical tests are often inconclusive, and following Humboldt's approach, we rely on the art of observation as our primary resource [1]. Patients themselves are the true experts of the disease: their narratives are indispensable. Only a genuine physician–patient partnership allows for a comprehensive understanding of the condition.

Since Descartes, subjectivity has often been relegated to the background [2], yet here it is the lived human experience that must guide our understanding of a phenomenon that continues to evade the standard instruments of modern medicine [3].

1.2 State of the Art of Knowledge

1.2.1 Loss as a Central Element in Long COVID

All patients with Long COVID share a common characteristic—loss—as illustrated in Figure 1.1, a word cloud generated from the narratives of the first 34 patients seen in my general practice in 2021 [4].Not always the same losses for everyone, nor all at once, but loss nonetheless. Loss of ability, loss of energy, loss of memory, loss of words, loss of balance, loss of taste and smell, loss of the body's automatic control systems, loss of sleep, and often loss of employment. Loss of social relationships, libido, intimacy, relationships with children, loss of their inner sense of self, and loss of trust in medicine.

Patients mourn for the lives they once had. Physicians who do not take the time to listen or truly hear often fill this void with unfounded diagnoses such as burnout or depression. Meanwhile, research progresses, and we now know we are dealing with a disease of staggering complexity. Viral persistence is no longer in doubt, with the virus attacking on multiple fronts—causing endothelial injury, generating autoantibodies, activating mast cells and platelets, and directly involving the intestines. All of this

Figure 1.1 – Patients' word cloud. Generated from the verbatim accounts of 34 patients seen in 2021. (M. Jamoulle) [4] The term *Loss* dominates.

compounds the sequelae of the initial infection, presenting an extraordinary scientific challenge [5].

1.2.2 Definitional Approach

WHO Definition (2021) In October 2021, the WHO established a clinical definition of post-COVID-19 condition using the Delphi methodology. According to the WHO, post-COVID-19 condition occurs in individuals with a history of confirmed or probable SARS-CoV-2 infection, three months after the onset of COVID-19, with symptoms lasting at least two months and for which no alternative diagnosis can explain these symptoms. The most common symptoms include fatigue, dyspnea (shortness of breath), and cognitive dysfunction (brain fog, memory, and attention disorders). These symptoms may persist after the initial infection, appear following a remission phase, or fluctuate over time [6].

CDC Definition (United States) The CDC defines Long COVID more broadly as:

> "The wide range of signs, symptoms, and health problems that persist or appear after an infection with SARS-CoV-2."

This definition encompasses a broad spectrum of clinical manifestations that can affect multiple organ systems [7].

Definition by the National Academies of Sciences, Engineering, and Medicine (NASEM) Among the many definitions already published, the one proposed by NASEM appears to be the most comprehensive:

> *Long COVID (LC) is a chronic condition associated with an infection (infection-associated chronic condition, IACC) that occurs after an infection with SARS-CoV-2 and persists for at least three months. It may present in continuous,*

relapsing–remitting, or progressive forms. Long COVID can affect one or more organ systems [8].

Long COVID manifests in multiple ways. A complete list of all signs, symptoms, and conditions observed in this disease would contain hundreds of entries. All organ systems may be affected, and patients may present with one or more of the following: shortness of breath, cough, persistent fatigue, post-exertional malaise, difficulty concentrating, memory loss, recurrent headaches, dizziness, elevated heart rate, sleep disturbances, problems with taste or smell, bloating, constipation, and diarrhea.

These conditions may appear as single or multiple diagnoses, including interstitial lung disease and hypoxemia, cardiovascular diseases and arrhythmias, cognitive disorders, mood disorders, anxiety, migraine, strokes, blood clots, chronic kidney disease, postural orthostatic tachycardia syndrome and other forms of dysautonomia, myalgic encephalomyelitis/chronic fatigue syndrome, mast cell activation syndrome, fibromyalgia, connective tissue diseases, hyperlipidemia, diabetes, and autoimmune diseases such as lupus, rheumatoid arthritis, and Sjögren's syndrome.

This definition could be refined in light of the recent findings presented in this report.

At present, it is almost certain that **Long COVID is a fluctuating, disabling, slowly evolving, multisystemic chronic viral disease with neurological tropism, with or without recovery, largely unknown to both the public and the medical community.**

1.2.3 Epidemiology of Long COVID

Post-COVID syndrome, or Long COVID, affects a significant proportion of patients after acute SARS-CoV-2 infection. A meta-analysis reports that, on average, 45% of people who survived the infection had at least one unresolved symptom approximately four months after infection. This prevalence is higher among hospitalized individuals (52.6%) than among non-hospitalized individuals (34.5%) [9].

A transnational survey of 10,615 people indicates an overall prevalence of Long COVID of 4.0% (95% CI: 3.6–4.5) in the general population and 8.0% (95% CI: 7.0–8.9) among those infected [10]. International studies consistently report a higher prevalence in women, particularly in persistent forms characterized by disabling functional symptoms.

Across the broader WHO European Region (53 countries), nearly **36 million people**—or about **3.6 % of the total population**—may have experienced an episode of Long COVID during the first three years of the pandemic [11].

In the 27-member European Union, prevalence was estimated at about **2.9 % in 2022**, corresponding to nearly **13 million people** affected [12].

It is well established that women are at higher risk of developing Long COVID than men. According to WHO Europe modeling, the risk is twice as high for women and is particularly elevated after severe disease requiring hospitalization (1 woman in 3 vs. 1 man in 5) [13].

A recent cohort study (RECOVER) estimated a relative risk of 1.31 (95% CI: 1.06–1.62) for women, even after adjustment for sociodemographic and clinical factors [14]. These values are consistent with those observed in our cohort.

1.2.4 Patient Experience–Centered Approach

Our perspective prioritizes the patient's holistic experience. It begins by observing a clear break from the patient's prior health status before COVID-19 infection and then examines underlying causes without preconceived alignment to known conditions. This approach allows for greater flexibility in recognizing emerging patterns or conditions that may not yet fit established diagnostic criteria.

References to epidemiological studies such as ComPare and RECOVER highlight the value of identifying symptom patterns that align with large-scale datasets, offering both validation and contextualization of findings through extensive research [15, 16].

Patients with Long COVID present with a wide range of symptoms, including fatigue, cognitive disorders (commonly referred to as "brain fog"), dyspnea, and neurological problems. These symptoms may fluctuate over time and frequently overlap, complicating the application of standard diagnostic criteria. Long COVID manifests through several hundred physical and psychological signs and symptoms whose prevalence varies across individuals. The absence of defined biomarkers further complicates diagnosis, making clinicians heavily reliant on patient-reported observations, which may be subjective and variable.

From a clinician's perspective, the natural course described by patients strongly resembles that of a fluctuating viral infection, similar to what is observed in certain cases of herpes or hepatitis B and C.

This situation underscores the need to adopt innovative approaches to effectively identify and manage Long COVID in primary care. Routine laboratory tests are often non-contributory, and repeated clinical encounters with similar presentations have prompted the search for additional sources of knowledge.

Moreover, symptoms may fluctuate over time, profoundly altering the patient's functional status with intermittent periods of remission. It is therefore essential to listen to patients and acknowledge the exceptional value of their contributions [17]. This approach is further explored later in this report.

1.2.5 Long COVID as an Exercise in Quaternary Prevention

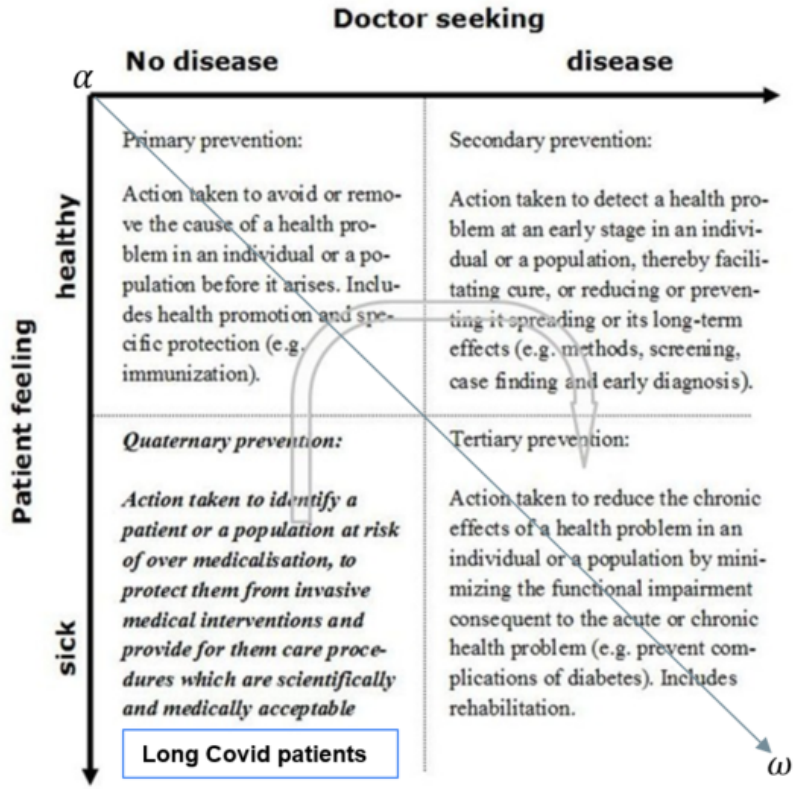
The relationship between physicians and patients is shaped by the encounter between lived experience and science—between the patient's awareness of being ill (or not) and the accompanying anxiety, and the physician's knowledge or uncertainty. From this interaction, we can derive a two-by-two table representing four fields, as shown in Figure 1.2 [18, 19].

One field involves a healthy patient meeting a physician in a non-disease context, such as for counseling or vaccination (box 1). Another arises when the physician suspects disease and pulls the patient toward early diagnosis or screening for a condition unknown to the patient (box 2). A third occurs when both physician and patient agree that disease is present—this is the realm of curative care as well as rehabilitation (box 3). Finally, there is the fourth quadrant: the patient feels acutely ill, yet the physician finds nothing and unsuccessfully tries to fit the patient into known diagnostic frameworks (box 4).

The first three boxes correspond to the classical definitions of primary, secondary, and tertiary prevention. The fourth quadrant, however, represents the domain of quaternary prevention: preventing harm from medical practice itself [20].

In the case of Long COVID, as we will see later, many patients remain **stuck in the fourth quadrant**: they are severely ill, do not understand what is happening to them, and often see their symptoms dismissed by physicians seeking to fit them into established

Figure 1.2 – Prevention model illustrating the intersection between the patient's experience and the physician's actions. The oblique timeline takes both patient and physician from *alpha* to *omega*, ultimately leading them to the same inevitable point: mortality. In the context of Long COVID, patients often remain trapped in the fourth quadrant—feeling ill while the physician fails to recognize the illness. To prevent this ordeal, the physician must engage in critical self-reflection regarding their own knowledge and biases. The central curved arrow signifies that the principle of quaternary prevention applies to all actions (Jamoulle, 1986) [18].



diagnostic categories. These patients feel abandoned by medicine and desperately seek help. The work undertaken by the scientists in the Long COVID network is therefore aimed at identifying the disease, naming it, describing it, elucidating its pathophysiology, and supporting patients. This research represents a concrete exercise in *quaternary prevention*, namely the prevention of harm caused by medical practice itself [21].

1.2.6 Impact of Long COVID and Perspectives

The consequences of the emergence of this new disease are profound. As Dr. Ziyad Al-Aly and colleagues have noted [22]:

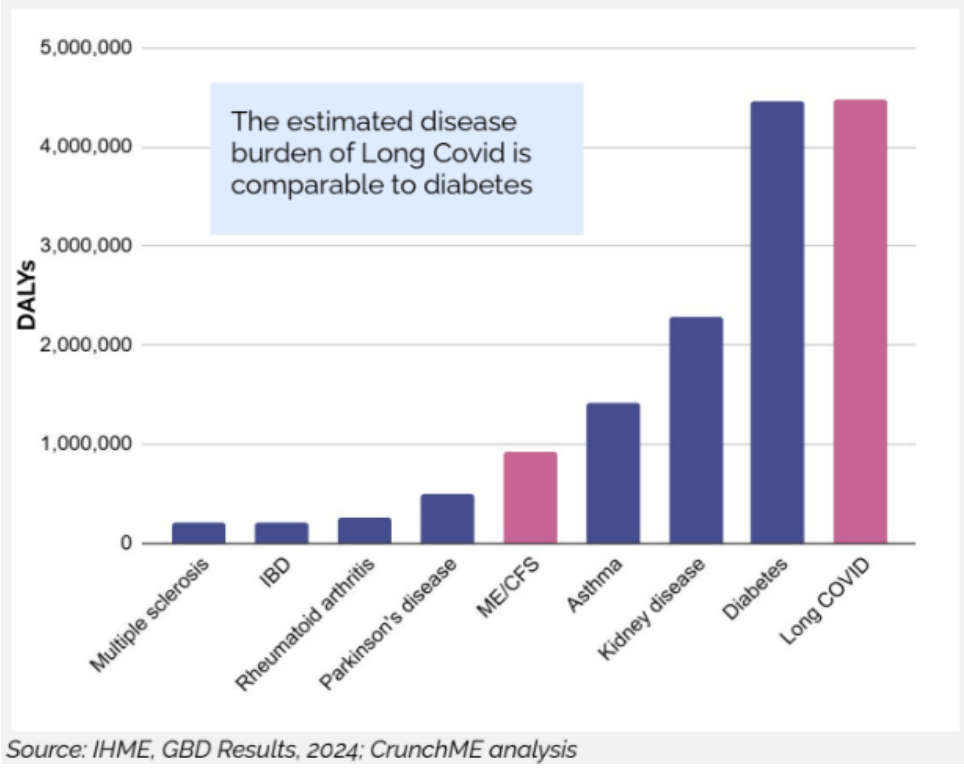
> *Long COVID can have devastating effects on individuals' lives and, because of its complexity and prevalence, it also has major repercussions on health systems and economies, even threatening progress made in achieving the Sustainable Development Goals. Meeting the challenge posed by Long COVID requires an ambitious and coordinated research and policy response strategy, which has so far been absent at the global level.*

In terms of quality of life and *Disability-Adjusted Life Years* (DALYs), the graph reproduced in Figure 1.3, published by a U.S. consumer association, is striking. DALYs measure the overall burden of disease by integrating both years lost due to premature mortality and years lived with disability.

Long COVID unfortunately ranks first, even ahead of chronic obstructive pulmonary disease (COPD), which is often linked to smoking and pollution.

It is also associated with a substantial loss of productivity at work; given the high number of people affected, this situation has major repercussions for health systems, the labor market, and the economy as a whole [23].

Figure 1.3 – Morbidity burden of selected diseases in the United States, measured in DALYs.



While significant budgets have been allocated at both the global and European levels to study the phenomenon and protect populations, in Belgium, little appears to be happening. Our institutions seem paralyzed: no dedicated research budget, no operational structure, no coordinated initiatives in medical faculties, hospitals, or public health agencies.

The national insurer has developed an administrative response, and some hospitals have opened "Long COVID" consultations or established online support systems. Yet this response remains inadequate and disappointingly modest compared to what is being done elsewhere in Europe. The Belgian medical and public health community seems frozen.

In contrast, while no public initiative has emerged, scientific mobilization has begun through the independent creation of a **Long COVID Research Network**, now fully operational in our country This report sets out the objectives and methods used to produce collaborative results drawing on diverse disciplines: clinical medicine, genomics, transcriptomics, proteomics, advanced immunology, neurobiology, imaging, computer and bioinformatics sciences, anthropology, and epistemology.

1.2.7 Current State of Knowledge on Long COVID: Toward Recognition of a Systemic Chronic Viral Illness

Post-COVID-19 syndrome, or Long COVID, is now recognized as a clinical entity characterized by the persistence or recurrence of symptoms several months after the acute infection. Its multi-organ involvement and fluctuating clinical manifestations highlight the complexity of its underlying pathophysiological mechanisms.

Recent literature, notably the omics review by Baalbaki *et al.* (2025), provides a comprehensive mapping of the biological alterations associated with post-viral syndromes, reinforcing the concept of a sustained systemic disorder.

Moreover, an emerging line of research implicates *Lipolysis Stimulated Receptors* (LSR) in viral persistence and possible SARS-CoV-2 reactivation in specific tissues [24]. This finding opens new avenues for understanding chronicity mechanisms at the molecular level.

Clinical Phenotypes and Biological Signatures

The work of Baalbaki *et al.* identifies several clinical phenotypes commonly observed in Long COVID: chronic fatigue, cognitive impairment, cardiovascular involvement, gastrointestinal disturbances, and dysautonomia. These clinical profiles correlate with distinct biological signatures, including persistent immune activation, oxidative stress, mitochondrial dysfunction, and metabolic dysregulation.

The Hypothesis of a Systemic Chronic Viral Disease

Multi-omics approaches reveal persistent transcriptional alterations and low-grade inflammation months after the initial infection, strengthening the hypothesis of a smoldering chronic infection. Converging evidence supports the existence of a viral reservoir—comprising RNA, proteins, or non-infectious viral particles—persisting well beyond the acute phase [25].

The primary sites implicated include the intestinal mucosa, lymphoid tissues, and immune-privileged compartments such as the central nervous system and testes. A landmark study from the Institut Pasteur demonstrated that SARS-CoV-2–infected hamsters exhibit a neurodegenerative molecular signature in the brainstem, with overexpression of innate immune response genes and altered expression of genes regulating dopaminergic and glutamatergic synapses, energy metabolism, and proteostasis [26]. These molecular alterations were accompanied by behavioral changes, including persistent depressive-like symptoms, impaired short-term memory, and late-onset anxiety features [27].

Our Contribution

Thanks to blood samples consented by many patients from the Charleroi cohort and other centers, the Long COVID Research Network has conducted transcriptomic, proteomic, immunophenotypic, autoimmune, and lipid metabolomic analyses, confirming viral persistence and elucidating the underlying mechanisms.

In parallel, members of the network have collected standardized clinical data essential for biostatistical analyses, while an anthropological approach has documented patients' lived experiences. At the same time, epistemological considerations have been integrated to critically examine the production and validation of knowledge surrounding Long COVID.

All of these works constitute the material of this volume.

1.3 Management of Patient Information: General Practice Facing the Structural Limits of the Belgian Health System

by Marc Jamoulle

General Practice in Belgium: A Shrinking Universe

General practitioners (GPs) in Belgium face growing bureaucratic constraints within an increasingly rigid healthcare system. Their technical and clinical roles are progressively reduced, often limited to administrative tasks such as writing certificates, attestations, or prescriptions. While supporting illness and suffering remains central to their mission, access to diagnostic tools—laboratory tests, imaging, or specialized procedures—remains largely controlled by hospitals and specialists, restricting GPs' capacity to exercise autonomous and integrated clinical judgment.

This reflects a national cost-containment policy that marginalizes primary care in favor of hospital-based medicine, which is viewed as the exclusive center of expertise and technological innovation. As a result, general practice is relegated to administrative triage rather than being recognized as a full partner in clinical care.

Table 1.1 – Diagnostic labels recorded for the first 50 Long COVID patients in the Charleroi cohort (2021–2022). Source: M. Jamoulle.

• Generalized anxiety disorder
• Angina pectoris
• Alzheimer's disease
• Pulmonary embolism
• Hyperventilation
• Fibromyalgia
• Traumatic shock
• Occupational exhaustion
• Panic attacks
• Post-traumatic stress disorder
• Depression
• Lazy adolescent (comment from a teacher)
• Irritable bowel
• Functional colopathy
• Burnout
• Malingering
• Autism spectrum disorder (comment from a psychiatrist)

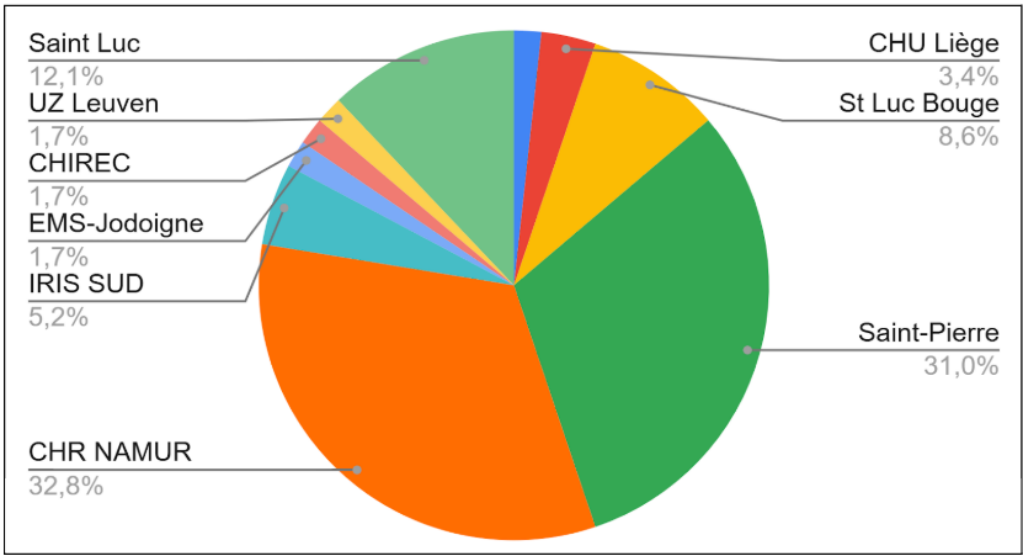
Despite these constraints, GPs occupy a unique position in the healthcare system through continuity of care and accumulation of information across multiple providers [28]. They are often the first to witness dysfunctions in the care process, as shown in Table 1.1 and Figure 1.4.

The Belgian national insurer explicitly recognizes this role on its *Long COVID Care Pathway* webpage:

> *The general practitioner plays a central role in supporting the patient throughout their treatment plan, ensuring regular follow-up and coordinating care with all providers involved, including those managing work incapacity.*

Yet, the annual remuneration of 25 euros per patient for care-pathway follow-up starkly contradicts this stated objective, reducing GPs' potential contributions to little more than formal declarations.

Figure 1.4 – Male, 29 years old, Master's student in the humanities. Acute COVID in 06/2020, two additional episodes in 2021 and 2023. Outpatient. Long COVID diagnosed in 02/2025. Technetium scintigraphy 03/2025: heterogeneous cerebral perfusion with multiple non-systematized focal hyperfixation areas, indicating SARS-CoV-2 encephalitis. Previously consulted in nine healthcare institutions across seven cities between June 2020 and January 2025. Excluding laboratory medicine, 38 physicians from 15 specialties were involved (source: Walloon Health Network Hub, Medispring software). M. Jamoulle consultation, 2025.



An Obsolete IT Network Presenting Itself as Innovative

The Health Network (Walloon, Brussels, Flemish), funded by the Belgian state to centralize health data, could have been a powerful tool for managing medical information. Technically secure and accessible to both physicians and patients, it nevertheless functions largely as a digital repository of scanned documents rather than a structured medical database. Information is stored without metadata, standardization, or analytical tools, making systematic use for research or clinical coordination extremely difficult.

Despite integrating international classification systems, very few physicians have received training in using them, leaving this vast database largely underutilized. As a result, searching for clinically relevant information often requires hours of manual review across fragmented records. Patients circulate between providers without effective coordination, as illustrated in Figure 1.4.

1.3.1 The Biographical Shift Induced by Long COVID and the Double Uncertainty

Long COVID often strikes individuals who previously considered themselves healthy, turning an acute infection into a profound biographical rupture. Even those with prior health conditions report a radical, unprecedented change in their physical and cognitive capacities. Basic daily activities become exhausting or impossible.

Patients struggle to make sense of this transformation. Without cultural or familial references to interpret their symptoms, some conceal them, internalize guilt, or misattribute them to psychological causes.

Physicians, confronted with atypical complaints that elude standard diagnostic frameworks, may underestimate or dismiss symptoms. Medical records reveal highly heterogeneous labels (Table 1.1), reflecting this diagnostic uncertainty. Over time, patients often

wander through multiple institutions, as laboratory results remain normal and advanced imaging inconclusive, leading eventually to psychiatric referrals when no alternative explanation emerges.

Where long-term physician–patient relationships exist, general practitioners may be the first to perceive this profound shift. Yet in Belgium's system of free specialist access, care remains fragmented by organ system rather than integrated around the patient.

Figure 1.5 – Acrylic painting by Nora Jamoulle entitled *Fog*. The work evokes both the scientific uncertainty faced by physicians and the cognitive fog experienced by patients, hindering communication as though both inhabit the same mist.

1.4 Partnering with Patients

Towards a new relationship with patients: contributions from the association, its pediatric group, and patient experts — Martin Spanoghe, Alexandre Muylle, Céline Decamp, Valérie Delcourt, Marie Coquel, Tomaso Antonacci, patient experts.

1.4.1 Long COVID Belgium ASBL

Long COVID Belgium is a non-profit association founded on February 20, 2024, by and for individuals affected by Long COVID. Its primary mission is to contribute to the recovery and improved quality of life of all those impacted by the disease. The association is led by patients themselves, with the active involvement of caregivers and parents of affected children.

As of March 2025, it brings together nearly 400 members and leads a much larger community through a highly active Facebook group counting 2,382 members.

The association's objectives, summarized in Figure 1.6 and presented on its website `https://longCOVIDbelgium.be`, include:

- Raising awareness and ensuring official recognition of Long COVID and its consequences;
- Securing research funding and facilitating Belgium's integration into international scientific networks and clinical trials;
- Achieving recognition of Long COVID as a chronic, serious illness, with patients designated as a high-risk population;
- Advocating for multidisciplinary care networks aligned with scientific advances, including the creation of specialized expertise centers;
- Supporting patients throughout their care journey, promoting autonomy, quality of life, and the defense of their rights.

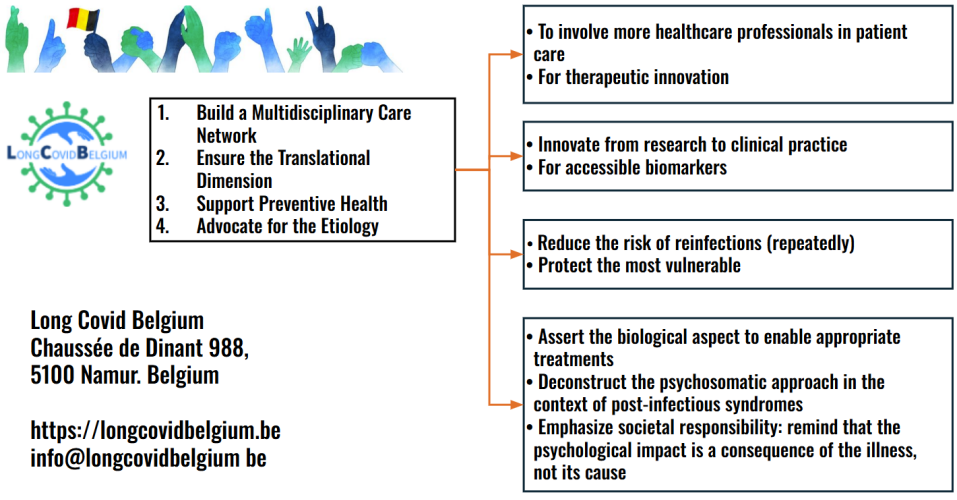


Figure 1.6 – Strategic priorities of the patient association Long COVID Belgium.

Contribution to the Long COVID Belgium Research Network

Long COVID Belgium plays an active role in the Long COVID Belgium Research Network, while ensuring strict compliance with patient rights and data protection regulations. Its main contributions include:

— Providing access to a patient cohort representative of the full spectrum of Long COVID symptoms in Belgium. These voluntarily engaged patients share experiences, respond to surveys, and participate in clinical research. A major questionnaire-based survey conducted between July and September 2023 has already produced valuable insights [29].

— Acting as a bridge between patients and other stakeholders. This two-way communication ensures that patients are informed about scientific progress, while researchers and clinicians remain connected to real-world patient experiences.

— Mobilizing patient experts trained by the *Patient Expert Center* (PEC) to co-design patient-centered healthcare services. `https://patientexpertcenter.be/fr`

— Leading public awareness campaigns to rally support and reduce the invisibility of Long COVID in society.

Advocacy for the Recognition of Long COVID: Achievements

Media visibility and collective mobilization. The association has contributed to numerous press articles, television reports, and public debates to increase awareness of Long COVID in Belgium.

A symbolic "lying down protest" organized in Brussels on March 15, 2025, in collaboration with Dutch-speaking patients, denounced the invisibility of Long COVID sufferers. The event received broad coverage in both French- and Dutch-speaking media.

Citizen petition. A citizen petition demanding urgent and sustainable funding for at least one dedicated Long COVID/Post-COVID expertise center — focused on biomedical research, diagnostics, and treatment development — has collected 2,151 signatures to date [30].

Political engagement. Ahead of the June 9, 2024 elections, a memorandum was addressed to political leaders at regional, federal, and European levels. It highlights:

— Severe deterioration in patients' quality of life,

— Insufficient access to adequate care,

— Progressive disengagement from health policy,

— And persistent denial within parts of the medical profession.

The document calls for urgent action through coordinated, evidence-based measures. Meetings with policymakers — including Ministers Vandenbroucke, Degryse, and Coppieters, as well as representatives from INAMI and KCE — have already taken place. At INAMI, the association specifically advocated for:

— Improved access to existing treatments,

— Official recognition of Long COVID as a high-risk condition,

— Extended consultation times supported by targeted training programs,

— Enhanced care pathways, especially regarding continuity and duration.

Tools and Data for Awareness and Action

Knowledge production and practical tools. Long COVID Belgium has produced several key resources for patients, practitioners, and policymakers:

— A **societal survey** entitled "Beyond the Symptoms: Social Implications and Barriers Faced by Long COVID Patients," presented at the symposium *Long COVID in Belgium: From Clinical Aspects to Public Health Consequences* (ULB, September 29, 2023). Based on 73 questions across six thematic areas, it collected responses from 367 participants. The full survey report provides a detailed analysis of the social repercussions of Long COVID [**longCOVID2023enquete**].

— **Amplifying the voices of children and adolescents** through projects such as the photo exhibition by Charlotte, one of whose works appears on the cover of this volume [31].

— Developing **an online practical guide for pediatric Long COVID** designed for families and educators. Created collaboratively by parents, young patients, healthcare professionals, and association members, it offers concrete strategies for supporting affected children [32].

— **Training patient experts** in collaboration with the Patient Expert Center (PEC). A first cohort of 17 patients is undergoing intensive training to become essential partners for clinicians, researchers, healthcare institutions, and policymakers.

1.4.2 A Patient Expert Shares His Long COVID Journey

By Bram Rolus, civil engineer & patient expert, Sint-Niklaas, Belgium

I was a working professional, married, father of three, passionate about sports. Running, tennis, and winter sports gave me energy and balance. In March 2020, I caught COVID-19. I stopped working for a few weeks to recover, never imagining that this seemingly mild infection would mark the beginning of a long and painful journey. This testimony is my story. It is personal, but it also resonates with that of many others. It is the account of what it means to become an expert in your own illness.

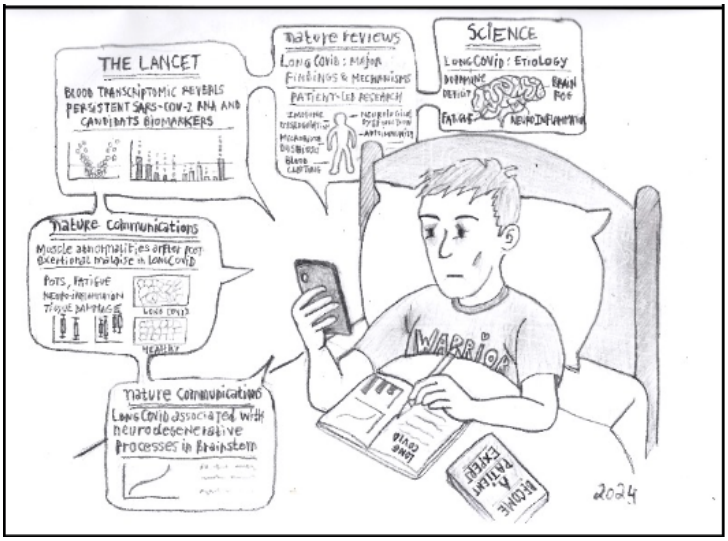


Figure 1.7 – Confined to bed yet driven by necessity, the patient turns to the internet and medical journals to decode a silent illness. © M.S.

When It Slips In Unnoticed

The acute phase passed, but I never truly returned to my former self. It didn't happen overnight—the change crept in quietly, like a thief in the night. Slowly, almost imperceptibly, I began to notice things slipping: a dull fatigue that lingered, moments of mental fog, a growing struggle to concentrate. Over time, the symptoms became harder to ignore—headaches, breathlessness, memory lapses. In 2021, I was reinfected. That was when the decline accelerated, and everything deepened.

The Temptation of Psychiatric Labeling

The first doctors suspected stress, burnout, even depression. I was told to rest, exercise, let go. But nothing helped. Every effort, even minimal, triggered a harsh relapse: muscle pain, fever, paralyzing fatigue. Climbing stairs was enough to make my heart race. The husband and father I had been slowly disappeared—like snow melting in the sun. And I felt myself sink into something no one seemed to understand.

With no clear medical answers, I began to chart my own path. I wrote everything down: symptoms, relapses, exams, consultations. Not out of obsession, but necessity. It gave me an anchor, helped me notice patterns no one in the traditional care system saw.

I have always been a precise person—my work demands technical accuracy and analytical thinking. Not being able to work at the same pace was hard to accept. But this need for clarity now helps me understand my illness and structure my recovery. I have been able to identify patterns and logics that no one else perceived.

Medical Practices Misaligned with Ethics

What hurts most is the contrast between my own sense of ethics—thoroughness, attentiveness, responsibility—and what I too often encountered in healthcare: rushed consultations, hasty judgments, erroneous diagnoses. My story was too often reduced to burnout, anxiety, or even hypochondria. Yet I had documented everything.

As the anthropologist Arthur Kleinman observes:

> *Physicians learn to treat diseases, not experiences; to repair bodies, not to address the experience of suffering. Yet this is precisely the experience patients want us to understand and respond to.* [33]

Between 2021 and 2024, I saw dozens of specialists: neurologists, psychiatrists, pulmonologists, cardiologists, therapists. My lungs, heart, blood, sleep, and brain were examined. Each time: "everything is normal." Yet I was no longer functioning. And it was clear that none of these doctors were reading the growing literature on Long COVID in their respective fields.

Two Readings of the Same Brain

In 2024, I finally had an isotopic brain imaging exam. For the first time, something was found: hypoperfusion in brain areas linked to memory, attention, and language. This explained the cognitive difficulties. A neuropsychological exam confirmed the disorders. For the first time, I felt heard.

But even then, nothing was simple. Two centers performed the same brain scan, with radically different interpretations. The first, a psychiatrist, concluded it was a psychiatric disorder: overcontrol, rumination, hypersensitivity. The second described clear cerebral hypoperfusion, consistent with a vascular form of Long COVID.

Same Exam, Two Diagnoses: Mental Disorder or Organic Sequelae?

How is this possible? For me, it was not just troubling—it was a demonstration of the central role interpretation plays in complex cases.

As Allen Frances points out:

> *There is no objective test in psychiatry—no X-ray, no lab result, no clinical marker that can confirm with certainty whether someone does or does not have a mental disorder. All diagnoses rely on interpretation.* [34]

When interpretation is neither rigorous nor validated, as is too often the case in psychiatry, we end up with uncertain hypotheses presented as certainties. Anything outside conventional frameworks is suspect. Anything challenging established dogma is taboo. New hypotheses, alternative approaches, and lived patient experience are too often dismissed.

Symptoms That Don't Seem to Belong Together

Fatigue is the most disabling symptom. It is not mere tiredness: it is a deep, total exhaustion that sleep does not relieve. Sometimes, a conversation drains me more than a walk. My executive functions are impaired. I take notes constantly, organize my thoughts meticulously, and rely on reminders to avoid mistakes.

I have learned to live with safety margins: just because I can do something does not mean I should. Rest has become a priority, even if it goes against social expectations.

I have always loved nature—the forests of the Ardennes are my refuge. Walking, breathing outdoors, is my way of reconnecting. But some days, even that is too much.

My social life has shrunk. I often cancel plans at the last minute. My children know that Dad needs rest. But they too deserve a present, attentive father. I constantly have to choose between what I can do and what I must give up.

When Systems Fail: The Case of Insurance

On top of the medical struggle comes financial pressure. As I am self-employed, working with my wife, we are well insured. Yet my income protection insurance fails to recognize Long COVID for what it is. Because the condition does not fit standard frameworks, decisions are often delayed or denied. It sometimes feels as if the lack of formal recognition works in their favor. That uncertainty places enormous strain on both our private and professional lives.

When the Medical System Fails, You Invent Your Own Science

What helps me today is having found caregivers who listen—the doctors and researchers of the Network mentioned in this report. They take the time. They consider that this illness may be a complex post-viral syndrome. It is thanks to them that I discovered the lipolysis-stimulated receptor (LSR) [35], a hypothesis involving lipid-mediated viral reactivation. This helped me understand certain symptoms, connections to diet, and neurological effects.

My illness has become a research project. My personal journal is more than a tracking tool—it is a source of care, perhaps even a contribution to this report. It is encouraging—finally, patients are being heard—but also sad: it took so much effort just to be acknowledged.

A Knowledge Community Born of Medical Neglect

My story is not unique. We are thousands. We are no longer just patients but researchers of our own cases. We read scientific papers, send samples to labs, analyze our own data. Not out of distrust, but because no one is doing it for us.

As Professor Fiona Jones and colleagues write:

> *People living with Long COVID helped shape research during the pandemic, and researchers must continue to acknowledge the importance of their contribution.* [36]

In recent months, I have begun to question many things in medicine. I have looked for mechanisms, cross-referenced data, asked new questions. Not out of despair, but because I have learned to see patterns where others do not.

My illness has become a research project. And all this while my brain craves rest, fighting information overload. It is a cruel paradox: the system expects me to comply, while my survival depends on understanding for myself what is happening.

This does not fit the traditional model where the doctor holds the knowledge and the patient must follow. But for me, that has never been enough. It was only when I was given the space to think, to question, that I could begin to build my own recovery.

I hope this testimony will not only contribute to the recognition of Long COVID, but also to a broader reflection: it is time to open medicine to new ways of healing.

Medicine that listens, that collaborates, that recognizes lived experience. Only under these conditions can we build human and sustainable care.

Chapter 2

Method

By Marc Jamoulle

Action research requires flexibility and continuous reflection [37]. It is often difficult to conform to the traditional format of a linearly structured study. In practice, successive observations and partial results modify the initial course of the work, revealing new methodological and conceptual challenges. Within this evolving movement, an interdisciplinary network of researchers gradually took shape in response to needs encountered in the field described in [38]. This dynamic—largely unforeseen at the outset—led to the mobilization of expertise from varied domains, ranging from clinical medicine to the social sciences, via multi-omics, advanced imaging, terminology, medical informatics, and data science. This informal network took the name *Long COVID Belgium Research Network*.

We can speak here of *participatory action research (PAR)* [39], which relies on a process of continual adjustment between methods used and results observed, within a dynamic of reciprocal learning. PAR is a systematic empirical investigation carried out in collaboration between representatives of the study population and researchers, with the aim of taking action or intervening on the questions or problems under study.

The evolving context of the research was also reshaped by the arrival of powerful technological tools, such as large language models (LLMs), which by 2023 had become indispensable instruments [40]. Extensively leveraged for their capabilities in text processing and terminological analysis, these models accelerated the processing of clinical records while opening new perspectives for structuring and deepening knowledge [41].

Long COVID, as a medical, social, and political phenomenon, raises complex challenges requiring integrated approaches and tools compatible with contemporary requirements for biostatistical analysis. With this in mind, standards such as the OMOP model (Observational Medical Outcomes Partnership) imposed themselves to ensure rigorous, harmonized, and reusable management of health data [42].

It is important to emphasize that, when this research was launched in July 2021, neither the extent of the Long COVID phenomenon, nor the massive influx of patients in diagnostic and therapeutic wandering, nor the rise of such an interdisciplinary research network were truly anticipated.

2.1 Continuous Acquisition of Scientific Knowledge

An Evolving Public Bibliography on Long COVID

In the era of Long COVID, medicine faces an unprecedented tension between the exponential production of biomedical knowledge and clinicians' ability to integrate it into daily practice. While fundamental research deploys tools of unprecedented power—from transcriptomics to metabolomics, including integrated multi-omics analysis—general practice and frontline clinical care must explore their concrete implications and engage in *more imaginative research*, as T. Greenhalgh notes [43].

Long COVID represents a multidimensional challenge for both patients and health professionals. Still poorly understood, it often remains invisible to caregivers, partly because of a rapidly expanding scientific literature that can overwhelm or disorient. To address this, we created an open, structured bibliography designed to organize knowledge in a way that reflects both clinical complexity and conceptual dimensions.

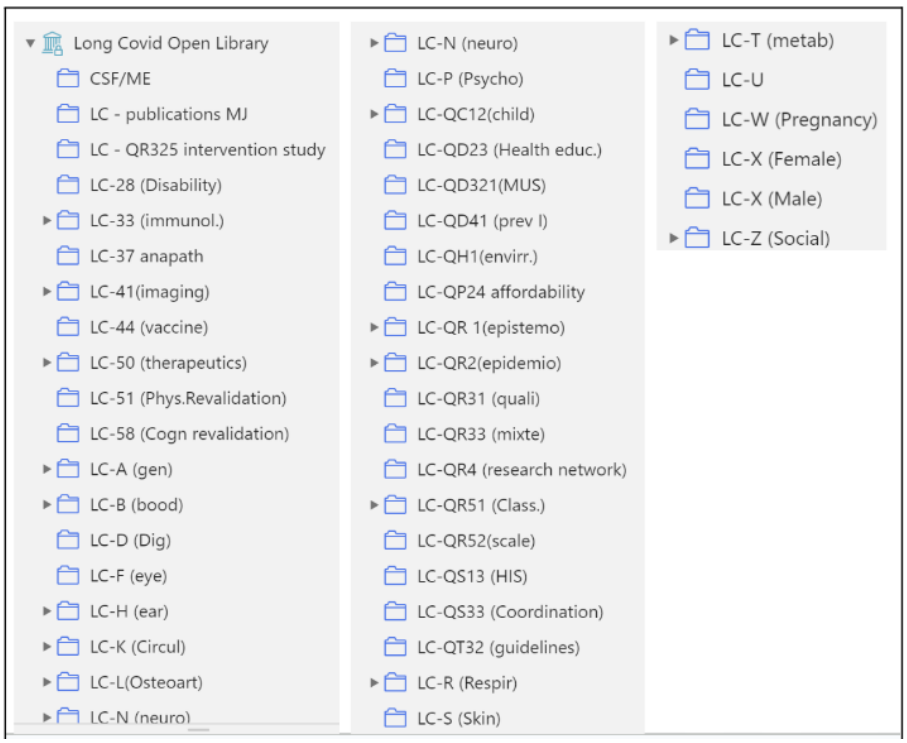


Figure 2.1 – Because Long COVID is a multi-system condition, nearly all ICPC chapters are represented in the bibliography, along with Q-Codes for conceptual dimensions. The letters from ICPC refer to body systems (A: general, B: blood, K: cardiovascular, Z: social, etc.), while Q identifies conceptual aspects [44].

The bibliography uses the *Core Content Classification in Primary Care (3CGP)* [45], combining:

— **ICPC-2**, structuring information into 17 chapters for different systems and organs (e.g., A: general problems, N: neurology, Z: social dimensions);

— **Q-Codes** [46], classifying conceptual dimensions such as access to care, representations, ethics, and epistemology.

Both tools are freely accessible via the HeTOP terminology server [47], providing a rigorous and evolving framework for indexing knowledge.

Since July 2021, a weekly literature watch has continuously updated this resource, managed with Zotero, a free open-source reference manager. References come primarily

from PubMed and Google Scholar, using descriptors such as *Post-Acute COVID-19 Syndrome [MeSH]* or *Long COVID [tw]*, yielding two to five new citations per week on average. Specialist social networks and direct exchanges with patients and colleagues further enrich this database.

Each article—or at least its abstract—is read, summarized, and archived in Zotero using its Google Chrome connector. Selection is made by a single observer according to clinical, epidemiological, diagnostic, or therapeutic interest and its relevance to ongoing research topics (multi-omics, neurobiology, imaging, qualitative research, etc.).

The resulting Long COVID Open Library is freely accessible online. Structured by both body systems and conceptual dimensions, it constitutes a living resource for researchers, clinicians, and patients alike [44].

2.2 General Practice Clinic and the Creation of the Cohort

As the first point of contact between the population and the health system, general practice occupies a unique position for detecting emerging health problems [48]. Its close proximity to patients, combined with continuity of care, makes it an especially favorable setting for conducting clinical research in real-world conditions [49]. As the European General Practice Research Network (EGPRN) emphasizes, *general practice/family medicine is the foundational discipline of primary health care and the cornerstone of many health systems in Europe* [50]. This central role enabled general practice to play a decisive part in the early recognition of Long COVID [51].

2.2.1 From the First Cases to a Structured Cohort

Starting in July 2021, we observed a growing number of patients whose lives were profoundly disrupted following an acute episode of COVID-19. The longitudinal perspective inherent to general practice—sometimes spanning several generations—made it possible to detect subtle yet persistent changes in health status.

One particularly striking case involved a patient whose severe symptoms improved dramatically after two doses of a COVID-19 vaccine. Although the manuscript describing this case was not accepted for publication, it remains publicly accessible [52] and marked the starting point for a broader research initiative.

As additional cases emerged, publications on the ORBI platform of the University of Liège attracted patients from across Belgium, far beyond our local practice in Charleroi.

This growing demand required a transition from informal note-taking to a structured research framework, integrating ethical standards, standardized questionnaires (e.g., *ComPaRe*), and digital tools for data collection, transcription, and analysis. Initial records maintained in Excel were ultimately migrated to a research database in *OMOP CDM* format, ensuring interoperability and enabling future large-scale analyses.

2.2.2 Internal and External Cohorts

Two distinct cohorts gradually emerged:

— **Internal cohort:** Patients from our historical patient panel, primarily from low-income neighborhoods (postal codes shown in red in Figures 2.2 and 2.3).

— **External cohort:** Patients from across Belgium, often with higher educational backgrounds (postal codes shown in blue in Figures 2.2 and 2.3), including some Dutch-speaking patients, with consultations conducted in English when needed.

This unusual recruitment pattern—where a neighborhood general practice attracts patients from across the country—highlights both the unmet clinical needs surrounding Long COVID and the structural gaps within the Belgian healthcare system for managing emerging diseases.

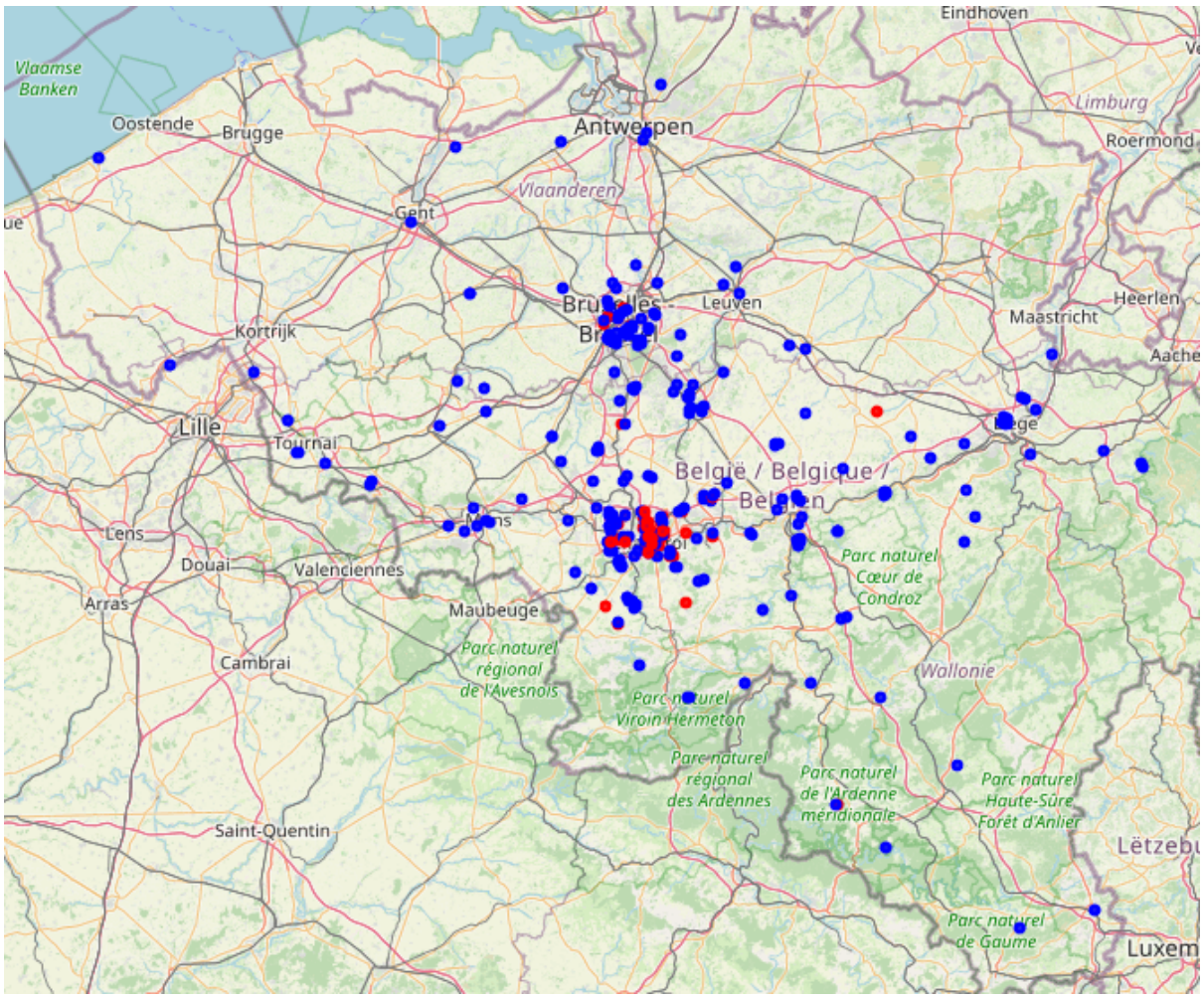


Figure 2.2 – Distribution of postal codes for patients consulting for suspected Long COVID. Red: 76 patients from the practice's historical panel. Blue: 249 patients with other primary care physicians. Status as of August 29, 2025 (Courtesy of Tarik Jamoulle, data engineer).

Writing the Patient's Story

For each Long COVID patient, following the method described above, we produce a structured narrative report including: (1) pre-infection history and record of prior morbidities; (2) acute episodes (dates of symptoms and/or RT-PCR results); (3) vaccination schedule and any adverse effects; (4) ComPaRe questionnaire and COOP/WONCA Charts; (5) HPO phenotypic list; (6) synthesis of specialist opinions (RSW hub protocols); (7) follow-up recommendations.

Sources include clinical records and an in-depth interview with the patient.

The completed report is first shared with the patient. It is then pseudonymized: all identifying information is removed, a non-meaningful alphanumeric code is assigned, and

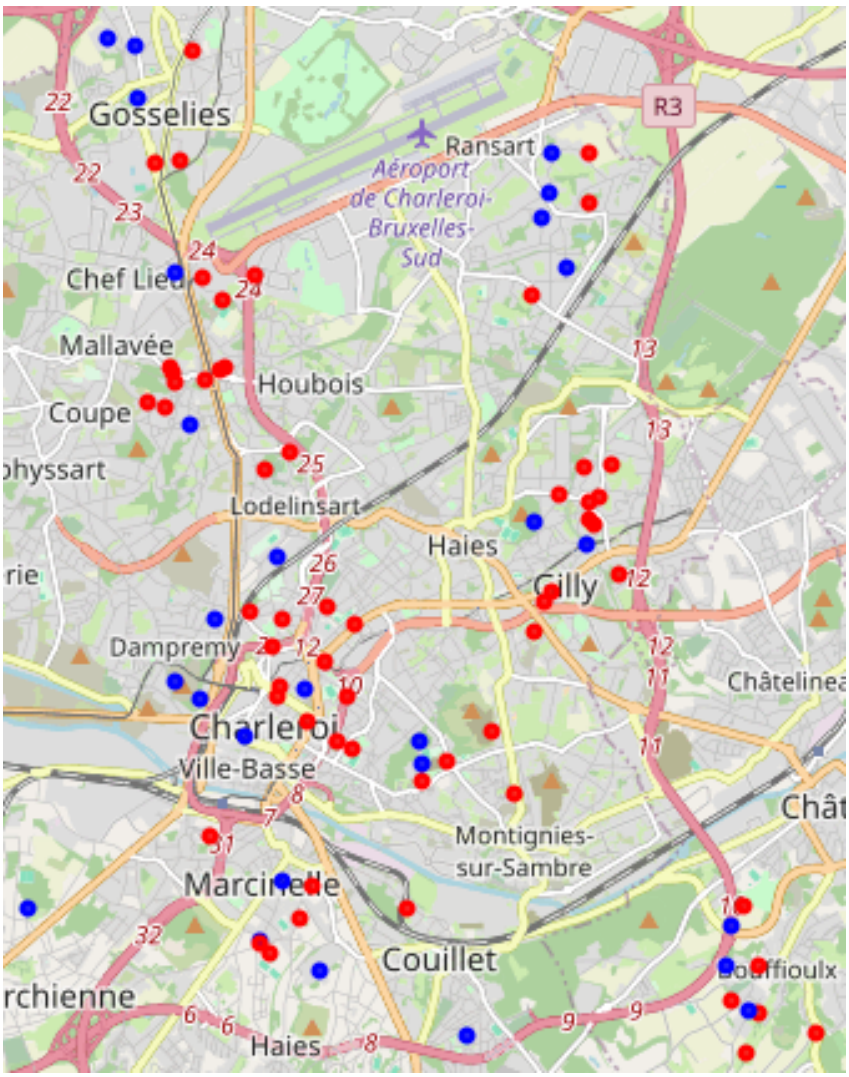


Figure 2.3 – Concentration of patients in Charleroi around the Cabinet médical Janson and surrounding areas. Blue: patients with other primary care physicians. (Courtesy of Tarik Jamoulle, data engineer).

the key is kept only by the investigating physician, in full compliance with the GDPR. All pseudonymized reports are stored in a secure database and made available to accredited researchers (see Appendix 6.1 for an example).

Patients are then referred, according to their specific needs, to the appropriate services within the care pathway organized by the national health insurer [53]. This may include neuropsychology, physical therapy, dietetics, or occupational therapy.

For patients living in Wallonia, a diagnosis of encephalitis provides access to specialized support from the association *Le Ressort* [54], which offers professional assistance to individuals with brain injuries.

2.3 Receiving Patients, Acquiring and Managing Their Information

For patients in the internal cohort (regular patients), the diagnostic orientation toward Long COVID is based primarily on clinical observations formulated by physicians themselves [55].

In contrast, within the external cohort, it is more often the patients who initiate the

diagnostic process. These individuals, frequently familiar with online medical resources or with scientific backgrounds, progressively develop the conviction that they have Long COVID and actively seek a health professional able to recognize and name their condition [56].

They are also typically sicker, have been ill for longer, and are profoundly affected by prolonged diagnostic uncertainty. This dynamic takes place within a therapeutic relationship built on mutual consent, a hallmark of general practice. In this context, confidentiality is implicit, and professional secrecy remains fully respected.

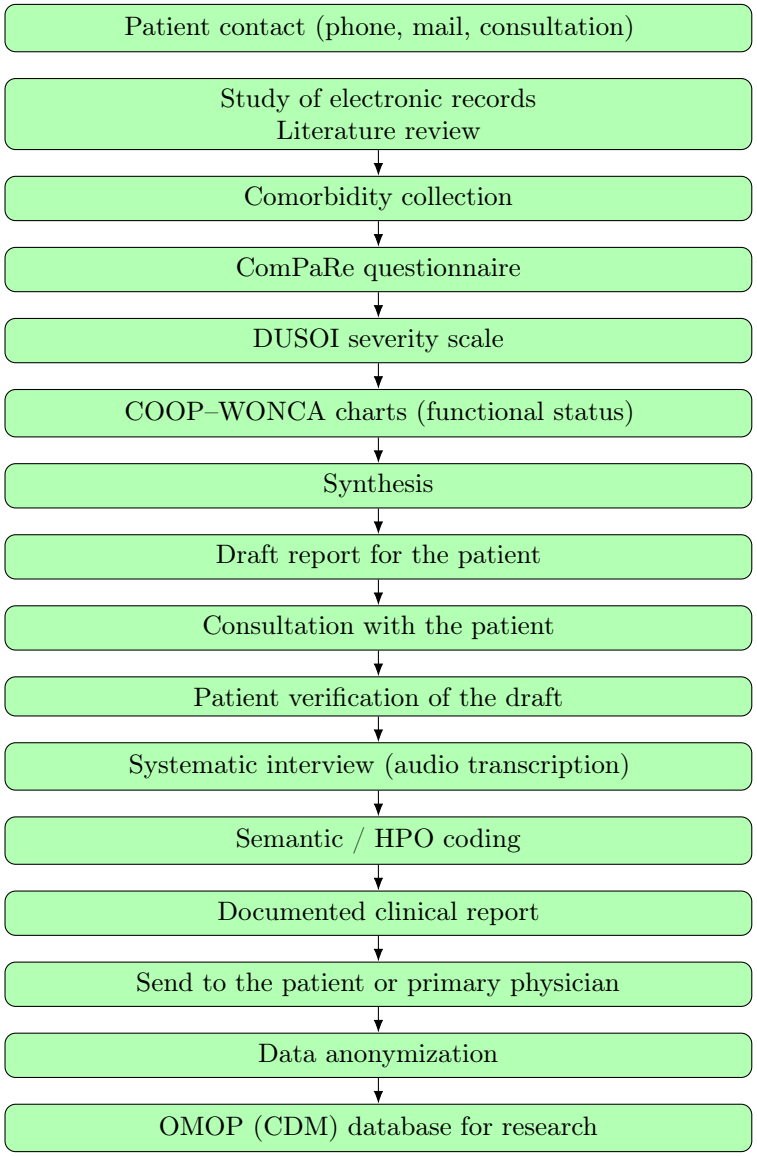


Figure 2.4 – Operational chain: from the first patient contact and initial data collection to the OMOP Common Data Model (CDM) research database.

2.3.1 Acquiring Information

For patients in the external cohort, an initial email is sent to collect the personal information required for secure access to their online medical records. Patients are asked to provide their national identification number and identity card number, in full compliance

with the legal and ethical framework governing medical confidentiality in Belgium.

Certified general practice software—Medispring, in this case—allows secure access to the Walloon Health Network Hub, where a medical record is created for each patient. Reports from specialists are retrieved and analyzed. An index of pre-existing health problems is established, along with a record of acute COVID-19 episodes, previous vaccinations, and any associated complications.

For health problems, the *International Classification of Primary Care, second revision (ICPC-2)* is used [57, 58]. Based on this information, a structured observation report is prepared, drawing on both medical records and responses to two standardized questionnaires (described elsewhere) sent electronically. An in-person consultation is then proposed, and the final report is forwarded to the primary care physician. An anonymized version is stored for research purposes (see Appendix 6.1).

Certified Belgian software integrates a secure data export protocol, the *Patient Migration Format* (PMF) in XML, allowing complete transfer of medical records between physicians when patients change providers. Once anonymized, these PMF files can be reused for research purposes.

Finally, research methods evolved substantially during 2023. Initially, the analysis of medical records was performed entirely manually, requiring a considerable time investment. The introduction of a large language model (LLM)—in this case, ChatGPT—profoundly transformed these practices. Used primarily for text analysis, this tool considerably reduced the workload associated with producing detailed medical records while improving both the speed and accuracy of symptom data processing.

2.3.2 Standardized Data Collection via Questionnaires

A questionnaire was developed based on the French *ComPaRe* study [59], a prospective cohort of adult patients with Long COVID. This cohort notably enabled the development and validation of a scientific tool to measure Long COVID severity, relying on patient-reported experiences and providing a fine-grained, longitudinal description of symptom evolution [15].

The questionnaire was made available online as an electronic form (*Google Forms*) and is completed by each external patient seeking a medical opinion. A unique alphanumeric identifier is assigned to each participant, ensuring full anonymity of collected data. The principal investigator is the only person authorized to link identifiers to patients' identities, in strict compliance with ethical standards.

Importantly, the patient's own perception of their illness plays a central role. Here, it is systematically collected and analyzed through standardized instruments. Both the initial contact questionnaire and the functional indicator questionnaire (cf. infra) are publicly accessible on the ORBI platform of the University of Liège [60].

2.3.3 Global Indicators of Severity and Functional Status

The need to quantify both the severity assessed by the physician and the functional loss reported by the patient leads us to use two complementary instruments commonly applied in general practice.

DUSOI

Alongside patient-reported outcome measures (PROMs) capturing the patient's perspective, the *Duke Severity of Illness Index* (DUSOI) provides a standardized clinical

assessment of severity established by the physician. Validated by Parkerson *et al.* [61, 62], this tool combines four dimensions:

1. Symptomatic state
2. Complications
3. Prognostic risk
4. Therapeutic difficulty

Each dimension is scored from 0 (absent) to 5 (extreme), producing an overall score that reflects both the current intensity of the disease and the anticipated complexity of care.

In Long COVID patients, DUSOI enables:

— Objective ranking of multi-system presentations (e.g., dyspnea, dysautonomia, cognitive dysfunction, cardiovascular disorders),

— Identification of comorbidities influencing prognosis,

— Longitudinal follow-up of complex clinical trajectories.

When used in conjunction with *COOP/WONCA charts*, which capture the patient's own assessment of functional status, DUSOI offers a **dual perspective**:

— The lived impact reported by the patient,

— The clinical severity assessed by the physician.

This complementarity supports prioritization, planning of specialized investigations, and the rational allocation of rehabilitation resources. Furthermore, it provides reproducible outcome markers for research and evaluation of interventions.

Given the polymorbidity, symptom fluctuation, and lack of reliable biomarkers in *Long COVID*, DUSOI offers a structured framework to **objectify severity**, track disease evolution, and inform both clinical and research decisions.

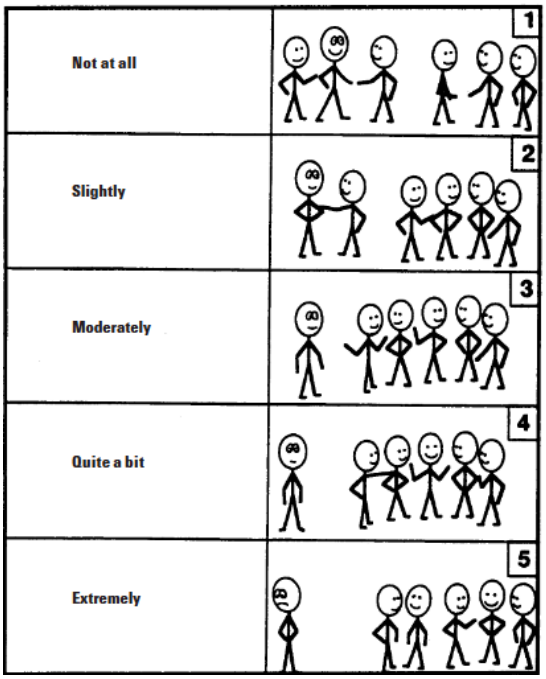


Figure 2.5 – COOP WONCA chart about social activities; *During the past 2 weeks... Has your physical and emotional health limited your social activities with family, friends, neighbours or groups*?

COOP/WONCA Charts as Functional Status Indicators

In the management of patients with Long COVID, the systematic integration of *patient-reported outcome measures* (PROMs) [63] is indispensable. Such tools allow the illness to be understood through the lens of the patient's lived experience and functional status, beyond biological or imaging parameters alone. The dominant symptoms of Long COVID—fluctuating fatigue, exertional dyspnea, cognitive disturbances, or diffuse pain—are profoundly subjective, vary over time, and affect quality of life, social participation, and return to work. These dimensions can only be fully captured through the patient's own voice.

Among the available instruments, the *COOP/WONCA* charts are particularly well-suited:

— brief (six items) and validated in primary care [64],

— specifically designed for general practice [65, 66, 67],

— simple to administer, either self-completed or filled out during consultation,

— covering key domains such as physical condition, daily activities, social performance, pain, emotional state, and perceived health.

The COOP/WONCA charts express the patient's subjective perception of their health in a simple visual format (Figure 2.5). This design promotes comprehension—even in exhausted or polysymptomatic patients—and its sensitivity to change allows longitudinal monitoring and supports personalized care plans based on shared decision-making.

Putting the COOP/WONCA charts online (available here [60]) in a Google Form, completed at home using the same identifier as for the *ComPaRe* questionnaire, provides two key methodological advantages:

1. **Continuity and traceability:** Data from multiple instruments can be paired for longitudinal analyses.
2. **Reduction of bias:** Self-administration outside the clinical setting minimizes the influence of healthcare professionals and reduces the well-documented social desirability bias [68], in which patients tend to present an overly favorable picture of their health status.

This approach reinforces the internal validity of measurements while preserving the simplicity and speed of use that make the COOP/WONCA charts so valuable for monitoring Long COVID patients.

Combining a clinician-assessed severity index (DUSOI) with a PROM such as the COOP/WONCA charts thus ensures a holistic, reproducible, and longitudinal assessment—an essential prerequisite for understanding and managing this complex, heterogeneous, and prolonged condition.

2.3.4 Managing Information

Limits of ICPC-2 and Use of HPO for Long COVID

The *International Classification of Primary Care—Second Edition (ICPC-2)* is above all a classification, that is, a conceptual filing tool based on physicians' reflection and interpretation. The Human Phenotype Ontology (HPO) [69] belongs to the domain of ontologies: it is a structured set of concepts, accompanied by their synonyms and hierarchical relationships, designed to be used directly by computer systems (see Figure 2.8).

ICPC-2 shows limitations when it comes to describing the clinical complexity of Long COVID, characterized by marked symptomatic heterogeneity, often with subjective, evolving, multi-system manifestations. To address these constraints, we used fine-grained symptom indexing with HPO, which offers a rich terminology specifically designed to describe human phenotypes. This indexing is not natively integrated into electronic medical records; it was performed a posteriori using a large language model (LLM), namely ChatGPT, after rigorous anonymization of textual data from patient records, according to the method developed by AP-HP. [70]

Figure 2.6 illustrates the validation pipeline for phenotype labels generated by LLM. The terms proposed by the model are compared with HPO entries by calculating semantic similarity (cosine); valid matches (threshold > 0.80) are then mapped to SNOMED CT and integrated into the OMOP CDM 5.4 model. This method, developed and validated by O. Latignies (URSP-ULB) and V. Angenot (University of Liège), helps limit coding errors related to language model hallucinations.

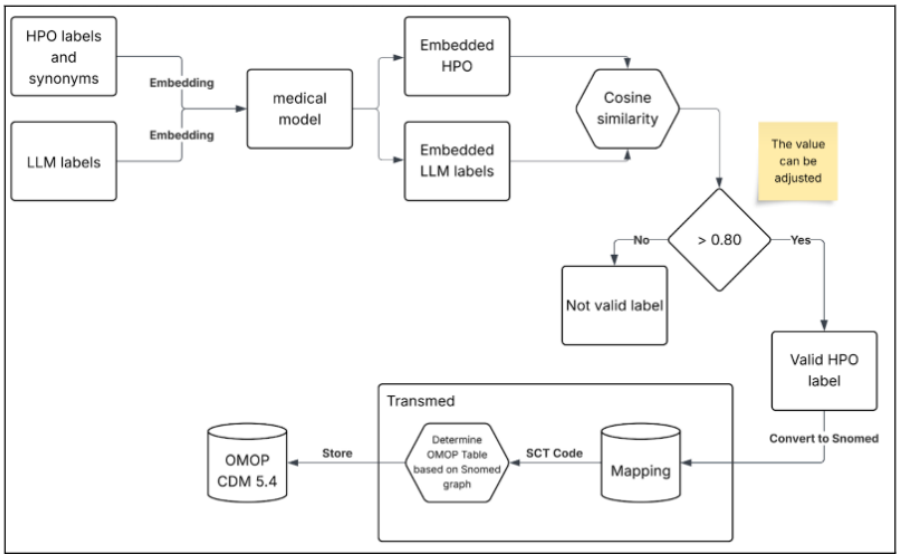


Figure 2.6 – Validation pipeline for HPO labels generated by LLM using semantic similarities. Valid matches are mapped to SNOMED CT and then integrated into the OMOP CDM 5.4 model (work by O. Latignies).

Thus, automated coding by LLM proves generally satisfactory from a semantic standpoint, with HPO terms matching patients' formulations well. However, coding errors and false positives require semi-automatic validation to ensure compliance with ontological standards used in clinical research.

Patients' Words Transformed by a Symptom Ontology

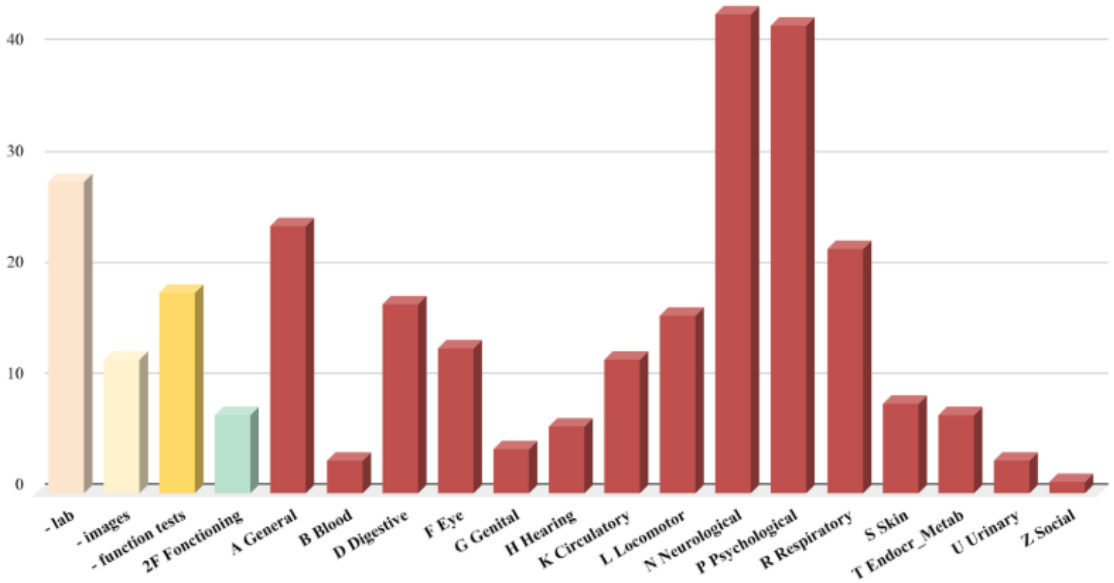
Faced with the repetition of unexplained clinical manifestations in patients well known to their physician and whose life course is profoundly altered, an in-depth exploration of the literature and of medical terminologies became imperative. Through this work, the unprecedented picture of Long COVID gradually emerged.

An ontology, beyond a simple dictionary, is a formal and explicit structure that describes the concepts of a domain and the relations that unite them. [71] It integrates logical axioms that allow automated reasoning and semantic interoperability, particularly in natural language processing (NLP). Ontologies such as SNOMED CT, HPO, or ORDO

thus provide a conceptual anchoring for entities extracted from clinical texts, ensuring uniform interpretation regardless of linguistic variations. [72]

In 2021, Deer *et al.* proposed a Long COVID–specific ontology based on HPO after analyzing 47 scientific publications. [73] This work led to the construction of the *Long COVID Phenotype Ontology (LCPO)*, comprising 286 entries. The ontology was then cross-linked by us with ICPC-3, English version [74], offering a bridge between Long COVID phenotypes and general practice codes.

Figure 2.7 – The 286 entries of the ontology developed by Deer et al. (2021) [73] mapped to the chapters of ICPC-3 [74]. This work (M. Jamoulle and K. van Boven, Radboud University Nijmegen) reveals a high prevalence of neurological, psychological, respiratory, and digestive symptoms.



This mapping of concepts present in HPO and ICPC highlights the multisystemic nature of Long COVID. Examining Figure 2.7, we see that bibliographic citations cover all body systems, including Psychological (P) and Social (Z), with a clear predominance for the brain (P and N), and underscores the predominance of neurological and psychiatric manifestations. This study also led us to use these same codes for organizing the bibliography.

2.3.5 Analysis of Patient Verbatim and Emails

In the external cohort, emails sent by parents often contain clinical descriptions that are already highly evocative. For both cohorts, symptom elements from exchanges with patients are recorded anonymously, with their explicit consent. This collection during patient interviews is carried out using a Google Pixel 6 smartphone equipped with an automatic transcription system or a Sony recorder, with subsequent transcription via `vook.ai`.

The anonymized textual transcriptions (verbatims) are first centralized in a Google Docs document to ensure traceability and ease of review. They are then transferred to the ChatGPT model using a prompt specifically designed for this task (reproduced in Appendix 6.3). This prompt guides the model in identifying described symptoms, indexing them, and classifying them according to a reference medical ontology—in this case, the Human Phenotype Ontology (HPO) [75, 69].

Using HPO serves a dual objective:

— **Structuring clinical diversity**, by capturing verbatims through controlled language that reduces the ambiguity of patients' spontaneous descriptions.

— **Ensuring semantic interoperability**, so that collected data can be used consistently by different clinicians, researchers, and information systems.

The *Human Phenotype Ontology* (HPO) is a hierarchical, standardized vocabulary designed to describe human phenotypic abnormalities in a comprehensive way. Each term corresponds to a precise clinical manifestation, endowed with a unique identifier (e.g., dyspnea `HP:0002094`), in which `HP:` denotes the *domain space* specific to the ontology, followed by **seven numerical digits** uniquely assigned to identify the concept. Thus, a term is linked to a concept, and this concept is identified by a stable alphanumeric string that allows computer systems to interoperate. Terms are organized by relations of generality and specificity, making it possible to navigate from the broadest symptoms to the finest subcategories.

Figure 2.8 – Example of an Excel cell listing the signs and symptoms from a patient encounter. Each item, separated by a semicolon, combines the standardized HPO term (English), its HPO code (URI), and the patient's verbatim (in Dutch) in parentheses. Illustration from a database of more than 300 similar sets.

Tremor (HP:0001337) [Tremoren bij activiteit of vermoeidheid] ; Post-exertional malaise (HP:0030973) [Post-exertionele malaise, trage recuperatie] ; Cognitive impairment (HP:0100543) [Brain fog, desoriëntatie, vergeetachtigheid] ; Anomia (HP:0002377) [Moeilijkheden om woorden te vinden] ; Impaired short-term memory (HP:0033687) [Korte-termijn geheugenstoornissen] ; Transient amnesia (HP:0011097) [Tijdelijke blackouts, verlies van oriëntatie] ; Ataxia (HP:0001251) [Coördinatieproblemen] ; Metamorphopsia (HP:0032080) [Visuele vervormingen (Alice-in-Wonderland-syndroom)] ; Hearing impairment (HP:0000365) [Gehoorverlies] ; Tinnitus (HP:0000360) [Tinnitus, inclusief pulsatiel] ; Pulsatile tinnitus (HP:0008629) [Tinnitus, inclusief pulsatiel] ; Sudden hearing loss (HP:0031735) [Plots gehoorverlies] ; Vascular headache (HP:0002315) [Vasculaire hoofdpijn] ; Palpitations (HP:0001962) [Hartkloppingen bij opstaan] ; Postural dizziness (HP:0002321) [Posturale duizeligheid] ; Apnea (HP:0002104) [Apneu voor een scherm ("screen apnea")] ; Exertional dyspnea (HP:0002875) [Inspanningsdyspneu (trappen)] ; Chest pain (HP:0100749) [Druk op de borst] ; Arthralgia (HP:0002829) [Gewrichtspijn (vingers, handen, knieën)] ; Osteoarthritis (HP:0002758) [Rhizartrose (duimbasisartrose)] ; Muscle weakness (HP:0001324) [Intermitterende spierzwakte (linkerbeen)] ; Impaired balance (HP:0002138) [Evenwichtsstoornissen] ; Constipation (HP:0002019) [Chronische constipatie] ; Chronic fatigue (HP:0012378) [Chronische vermoeidheid]

Recourse to HPO thus facilitates not only standardized clinical description but also advanced computational use (automatic indexing, comparative analyses, integration with other biomedical databases). This approach represents an essential step in transforming patients' narratives into structured data that can be used both in clinical practice and in research. The analysis of a patient interview by LLM and HPO is illustrated in Figure 2.8.

2.3.6 Imaging and Blood Sampling for Research Purposes

Depending on the clinical state of patients, different paraclinical tests were prescribed to document Long COVID and to screen for possible complications. These included laboratory tests targeting the emergence of de novo diabetes, markers of autoimmune disease or coagulation disorders, as well as brain imaging.

Documenting Long COVID Through Imaging

The analysis of the Long COVID ontology by Deer et al. [73] (see Figure 2.7) highlighted a condition with a strong neuropsychiatric component. Brain exploration therefore naturally imposed itself as a central research axis. Recent literature from 2021, in particular the work of Verger and Guedj [76, 77], highlights—thanks to [^{18}F]FDG PET—significant

regional hypometabolisms correlated with cognitive disorders and persistent symptoms. These results support the hypothesis of diffuse functional brain involvement, notably in areas implicated in attention, memory, emotional regulation, and somatic perception. Other techniques, such as [^{11}C]PBR28 PET, allow evaluation of neuroglial inflammation and its correlation with peripheral markers [78].

Conventional brain MRIs most often remain normal, which contrasts with the intensity of reported neurological symptoms. Many teams nevertheless report the potential value of functional MRI, an exam not yet available in routine clinical practice in Belgium.

In Belgium, the indication for [^{18}F]FDG PET is limited to cases of suspected Alzheimer's disease at the request of a neurologist. In our practice, an alternative was to prescribe technetium brain scintigraphy, which provided particularly informative results: several patients exhibited clear cerebral perfusion disorders compatible with vascular encephalitis. These observations were reproduced many times. The difference between scintigraphy and PET is discussed in Chapter 4.5.

Technetium tomoscintigraphy coupled with computed tomography (SPECT-CT), more accessible than PET, also makes it possible to demonstrate cerebral metabolic abnormalities comparable to those observed in Alzheimer's disease or after a stroke [79]. SPECT-CT ECD Tc-^{99m} imaging, described as early as 1988 [80], is based on the use of technetium-99m, whose uptake is proportional to cerebral blood flow [81, 82]. This tracer, widely used in clinical practice, can be eliminated according to standard procedures and is more environmentally friendly than PET scanning.

In some cases, head CT and MRI were included in data collection. When no prior MRI was available, performing one was recommended in order to rule out stroke or other silent lesions.

Through collaboration with Dr. Jean-Marc Constans, head of neuroradiology at the Amiens University Hospital, several patients were also able to undergo magnetic resonance spectroscopy (MRS) (see Section 3.12). Other structural or functional MRI modalities can reveal brain changes, but they are not currently available in Belgium [83, 84, 85].

Participation in the international Long COVID congress organized in Barcelona in 2023 proved decisive. It was on this occasion that we met Dr. Constans and learned about ongoing research on MRS [86], an examination still unavailable in Belgium. This technique provides objective confirmation of post-COVID encephalopathy.

Functional MRI (fMRI) has likewise shown high value in the study of Long COVID and has been the subject of numerous investigations [87, 83]. Several patients in the cohort chose to travel abroad to access this examination at their own expense, as INAMI refused reimbursement on the grounds that it is not yet recognized within Belgian medical services.

2.4 Creation of the Long COVID Research Network

The *COVID Human Genetic Effort* (`https://www.COVIDhge.com/`) is an international consortium aiming to discover the human genetic and immunological bases of the different clinical forms of SARS-CoV-2 infection. By contacting this network, we were able to put the recent advances of molecular biology at the service of patients and research, in an attempt to bridge the gap between the new sciences and clinical practice.

Thanks to Professor Jean-Laurent Casanova, one of the founders of the consortium, we established links with molecular biology researchers in Belgium, Sweden, and France. The meeting between a frontline clinician and research laboratories proved very fruitful and marked the beginning of our own research network. Collaboration with Professor Isabelle Meyts, pediatric geneticist, and Professor Johan Van Weyenbergh, senior immunologist at the Rega Institute, also opened the way to a broader network of researchers in multi-omics and neurobiology.

The biobank of patient samples from Charleroi is a valuable resource for several studies: in proteomics (Prof. Bart Van Puyvelde, UGent), in advanced immunology (Brodin Lab, Karolinska Institute, Sweden), and in genomics (Dr. Aurélie Cobat, Necker Hospital, Paris).

Professor Charles Nicaise, neurobiologist at the University of Namur, and Ms. Margaux Mignolet, doctoral student, also joined the group for a study on patient autoantibodies and the genesis of pain.

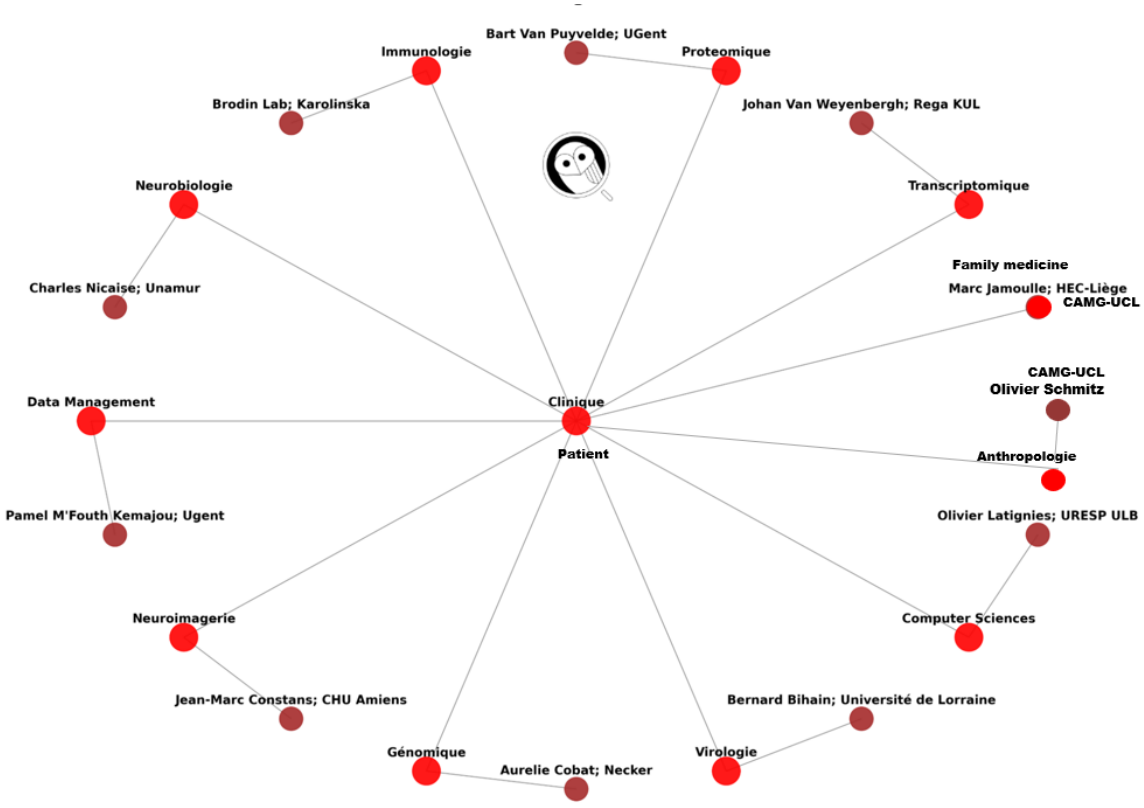


Figure 2.9 – Long COVID Research Network. The owl is the epistemologist in observation: a symbol of scientific questioning.

Since early 2025, Dr. Bernard Bihain, molecular biologist, and Mr. Pierre Florian, research engineer, from Genclis (Vandoeuvre-les-Nancy, France), together with Ms. Hélène Jeulin, virologist at the University of Lorraine in Nancy, have brought new expertise to the network.

The qualitative analysis of patients' lived experience is conducted by Ms. Kazeneza-Mugisha, medical student at ULB, and by Mr. Olivier Schmitz, anthropologist at CAMG (UCLouvain). In addition, magnetic resonance spectroscopy is performed in a subset of patients by Professor Jean-Marc Constans, head of neuroradiology at the Amiens University Hospital.

This network was built informally, out of shared necessity, around clinical care and participating patients. All of this took place without prior planning or dedicated coordination budget. Only curiosity and the passion to know and understand united the participants, all of whom contributed to this volume.

In the network image, behind the owl scrutinizing the network through its magnifying glass lies epistemology—the questioning of science that should animate every researcher.

2.5 Ethical Aspects

2.5.1 Funding and Conflicts of Interest

A Scientific Endeavor Driven by Volunteer Commitment

This research is above all a story of personal and collective commitment, carried by sincere, often discreet volunteerism. In 2022, the King Baudouin Foundation granted a personal award to Dr. Marc Jamoulle to launch the project. This support was unfortunately not renewed, as COVID was then considered "out of fashion." Thanks to the support of Drs. Guy Baele and Emmanuel André, who invited us to contribute to a special issue of the journal *Viruses*, we were nevertheless able to publish our first advances in the field of scintigraphy [52].

In the face of institutional disengagement, Dr. Johan Van Weyenbergh mobilized the remaining resources of his laboratory at the Rega Institute to continue the work. He invested tirelessly, sacrificing evenings and nights to analyze the first fifty blood samples generously donated by patients. This hard work resulted in a 2024 publication in *The Lancet Microbe* [88], which attracted the interest of two U.S. organizations dedicated to supporting research on Long COVID.

At that stage, our team was forced to pause analyses due to a lack of funds to acquire the necessary reagents. About one hundred samples thus remained pending, stored in the freezer, in the hope of better days. Only in the autumn of 2024, thanks to substantial funding from the PolyBio Research Foundation (US), were we able to order the reagents required for transcriptomic analyses and resume investigations.

Repeated appeals to Belgian institutions—ministries of health, KCE, Sciensano, and other agencies—unfortunately went unanswered. Research on Long COVID in our country seemed destined for indifference, as if an implicit watchword had been issued: "COVID is a thing of the past."

Since 2025, the company GENCLIS SA (Nancy, France), whose CEO is Dr. Bernard Bihain, has shown interest and provided support for our work.

Declaration of Conflicts of Interest Johan Van Weyenbergh has received funding from the Research Foundation–Flanders (FWO) via grants G0A0621N and G065421N, from the PolyBio Research Foundation, as well as from LCAP/LCF crowdfunding. Marc Jamoulle received a grant from the King Baudouin Foundation (2022-J51708200-F001). JVW also received speaker fees from Pfizer. Since August 2025, Dr. Jamoulle has become a consultant to Genclis SA and receives funding, as does Dr. Soylu. The authors declare no other conflicts of interest.

Funding Statement This study was financed by FWO grants 1278023N, G0A0621N, and G065421N; FNRS grants CDR J.0147.22, 1.E.140.24F, and 1E14024F2; a grant from the King Baudouin Foundation (2022-J51708200-F001); and by the Horizon Europe UNDINE program. Margaux Mignolet is supported by an FNRS/FRIA doctoral fellowship.

2.5.2 Research Ethics

ULg Ethics Committee – Descriptive Long COVID Study

The University of Liège hospital–faculty ethics committee stated, in an opinion dated January 27, 2022, that the descriptive and narrative study of Long COVID cases in general practice did not fall within the scope of the law of May 7, 2004, on human experimentation. No negative ethical opinion was issued.

Independent Ethics Committee UZ/KU Leuven

The COVID-19 resistance study, coordinated in Leuven by Prof. Isabelle Meyts (UZ/KU Leuven) in collaboration with the international COVID-HGE consortium, aims to identify genetic and immunological factors conferring protection against SARS-CoV-2. It particularly seeks to understand why some individuals, although highly exposed, do not develop the infection or present only asymptomatic forms.

This research is based on the collection of clinical and biological data from questionnaires and blood draws in infected patients or their relatives. Samples are analyzed to detect the presence of antibodies and to assess potentially protective immunogenetic markers. The study is strictly supervised ethically and legally, in accordance with GDPR requirements and Belgian law, with pseudonymization of data and traceability of informed consent.

No risky medical procedures are involved, apart from a single venipuncture. The results, coded and anonymized, may be published for scientific purposes. Biological samples are stored for up to 10 years for possible related research. Participation is voluntary, free of charge, and can be stopped at any time without consequence for care. Insurance covers any potential harm. The principal investigator, Dr. Marc Jamoulle, undertakes to respect the principles of the Declaration of Helsinki and good clinical practice.

UNamur Ethics Committee – Autoantibodies and Neurological Sequelae

This pilot study, conducted by CHU UCL Namur and the University of Namur, aims to search for autoantibodies directed against the nervous system in patients with Long COVID and neurological sequelae. It combines a standardized neuropsychological assessment with a blood draw (120 mL) for laboratory analyses. Data and samples are processed anonymously and stored for 10 years. Participation is voluntary, without impact on the quality of care, and governed by Belgian and European regulations on data

protection and human research. The study was approved by the CHU UCL Namur ethics committee.

The hospital–faculty ethics committee of CHU UCL Namur (Godinne site) approved, in May 2023, an amendment to the protocol of the single-center study entitled "Study of the Pathogenicity of (Auto-)Antibodies in Patients with Long COVID and Neurological Sequelae," led by Profs. Pierre Bulpa and Charles Nicaise. This approval concerns the updated version of the protocol and the information and consent documents, in compliance with Belgian law of May 7, 2004, on human experimentation and ICH/GCP guidelines. The committee recalls the personal responsibility of the principal investigator in the conduct of the study.

2.5.3 Confidentiality, Pseudonymization, and Research

Secure Extraction of Health Data

Research on Long COVID relies on the ability to collect and analyze personal health data—often sensitive—derived from general practice consultations. This reality raises crucial issues of confidentiality, security, and ethics. In Belgium, extracting such data from software used in frontline care, such as Medispring, makes the use of pseudonymization or anonymization tools indispensable, whether for quantitative information (results, scores, timelines) or qualitative information (expressed symptoms, narratives, interview transcripts).

Identifiable entities in clinical documents targeted by the EDS Pseudo system

• **ADRESSE**	Street address, e.g., 33 boulevard de Picpus
• **DATE**	Any absolute date other than a birthdate
• **DATE_NAISSANCE**	Birthdate
• **HOPITAL**	Hospital name, e.g., Hôpital Rothschild
• **IPP**	Internal AP-HP identifier for patients, displayed as a number
• **MAIL**	Email address
• **NDA**	Internal AP-HP identifier for visits, displayed as a number
• **NOM**	Any last name (patients, doctors, third parties)
• **PRENOM**	Any first name (patients, doctors, etc.)
• **SECU**	Social security number
• **TEL**	Any phone number
• **VILLE**	Any city
• **ZIP**	Any zip code

In this respect, the initiatives implemented by the Assistance Publique–Hôpitaux de Paris (AP-HP) are a useful reference. AP-HP has developed a Health Data Warehouse (Entrepôt de Données de Santé, EDS) bringing together data on more than 13 million patients. To ensure security, two approaches are used:

— **Pseudonymization**: replacing identifying data with codes, while preserving the possibility of re-identification by authorized managers only.

— **Anonymization**: removing any information that could identify an individual, making re-identification impossible.

In 2023, AP-HP validated a natural language processing algorithm to pseudonymize clinical documents automatically. This hybrid system, combining deep learning and expert rules, achieves remarkable performance (F1-score of 0.99). It allows secure access to textual data, in compliance with medical confidentiality, and thus promotes responsible research [89]. Technical details and source code are openly available on the AP-HP EDS-Pseudo GitHub platform, paving the way for adaptations in other clinical contexts, including general practice.

Within this framework, and during data extraction from consultations or electronic medical records, our team uses analogous procedures to ensure patient protection. Structured reports or transcripts from clinical interviews undergo rigorous processing to preserve privacy, in line with European best practices in ethics and data security.

Chapter 3

Results

3.1 Description of the Long COVID patient cohorts followed at the Janson Medical Practice, Charleroi

by Marc Jamoulle

3.1.1 Cohort distribution

As of **August 15, 2025**, the cohort initiated in **July 2021** includes a total of **329 patients**, of whom **222 women** (67.5%) and **107 men** (32.5%).

Figure 3.1 shows the distribution of patients by sex and type of primary care physician. Among **women**, 79.3% (176/222) are followed by **external** physicians and 20.7% (46/222) by **internal** physicians, meaning physicians from the Janson Medical Practice. Among **men**, 72.0% (77/107) are followed by **external** physicians and 28.0% (30/107) by physicians from the Janson Practice.

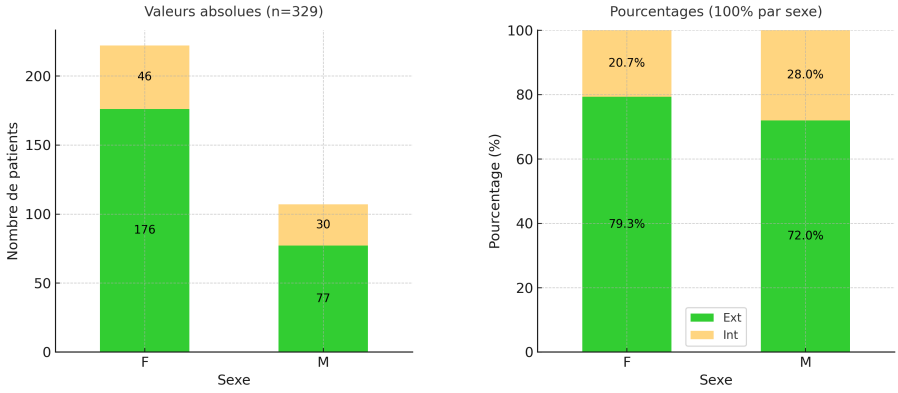


Figure 3.1 – Distribution of the cohort (n=329) as of August 15, 2025, by sex and type of primary care physician. Absolute values are shown on the left and percentages (100% by sex) on the right.

Figure 3.1 shows the situation observed at the time of writing this paper. The analyses presented below specifically concern the status of the cohort as of July 1, 2025, when it included 307 patients, as shown in Figure 3.2.

On July 1, the first cohort consisted of 70 so-called "internal" patients, followed long-term at the Janson Medical Center, located in a working-class neighborhood of Charleroi marked by the legacy of deindustrialization. These patients, well known to their general practitioners, mostly live in hardship, often aggravated by drug addiction or dependence on social assistance programs. Their education level is generally low, with few

having completed higher education. However, their close relationship with their physicians enabled rapid detection of health deteriorations after the acute phase of COVID-19.

Among 70 patients identified as having long COVID within our practice, the course three years after the acute phase was heterogeneous: about one-third had regained satisfactory health, with post-COVID fatigue and associated symptoms only a memory; another third resumed an almost normal life but retained sequelae, mainly memory disorders; finally, nearly one-third remained severely affected, completely unable to resume professional or social activities.

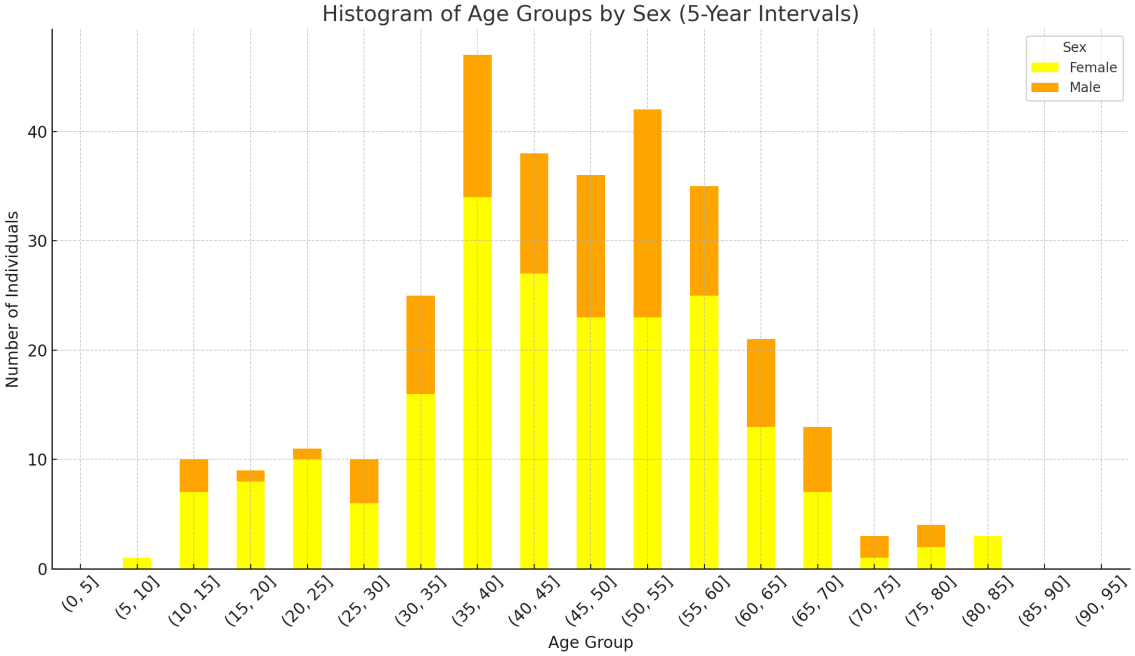


Figure 3.2 – Age and sex distribution of all consulting patients clinically affected by long COVID (307 people as of July 1, 2025). Women: 67%. Youngest patient: 6 years, oldest: 83 years. Consultations, Charleroi. Dr. Jamoulle and Dr. Zayane, 2021–2025.

The second cohort consists of 237 so-called "external" patients who, after a long journey to access care, came to consult in Charleroi. Their socioeconomic profile contrasts sharply with that of the internal patients: they are mostly highly educated individuals working in cognitively demanding professions — lawyers, physicians, architects, IT specialists, psychologists, or corporate executives. Before the onset of symptoms, no sign of economic vulnerability was apparent. Possessing significant intellectual resources, these patients extensively researched online and mobilized their networks to understand a severe symptomatology long ignored by primary care medicine. At their first consultation at the Janson Medical Center, most were on prolonged sick leave, indicating major functional impairment despite their high socio-cultural capital. In contrast with the local cohort, the illness remained severe over time for most of these patients.

Thus, the two cohorts differ clearly, both in socioeconomic context and in post-COVID-19 clinical trajectory. Age group analysis further shows that most patients belong to the working-age population.

Within the cohort, there are also:

— 1 infant (born after maternal COVID infection during pregnancy),

— 1 child aged 6 years,

— 8 children aged 10 to 15 years,

— 9 adolescents aged 15 to 20 years.

These children and adolescents have been ill for an average of about four years, reflecting the marked chronicity of the condition. An illustrative example is shown in Figure 3.8. A specific cohort of ten children, aged 7 to 16 years, is the subject of a dedicated analysis and is presented in detail in the Results section (see Section 3.5).

3.1.2 Gender-based Analysis of Long COVID Distribution in Two Clinical Cohorts

The comparison of the internal and external cohorts provides insight into the gender dynamics at play in the epidemiology and recognition of long COVID. Across both groups, there is a clear overrepresentation of women, with a ratio of more than two women for every man. This distribution is consistent with trends reported in other long COVID studies [90].

Several factors may contribute to this disparity:

— **Biological factors:** Women generally have stronger immune reactivity, which may favor prolonged inflammatory or autoimmune responses.

— **Societal factors:** Women tend to consult more frequently for functional disorders and are more likely to verbalize chronic suffering.

— **Medical and structural factors:** Recognition of Long COVID often depends on self-reported symptoms; prevailing notions of the "credible patient" may privilege certain gendered profiles, reinforcing diagnostic bias.

— **Masculinist bias in medicine:** The medical field has historically been shaped by male-centered perspectives, with clinical trials and diagnostic frameworks often built around male physiology. This structural bias may contribute to under-recognition or trivialization of women's symptoms in conditions such as Long COVID.

This gender imbalance, far from being a methodological artifact, underscores broader structural health inequalities. It must be taken into account in the organization of care, the design of research protocols, and the development of public health policy. Overall, the marked predominance of women in both diagnosis and follow-up calls for a differentiated, gender-sensitive approach to better understand and treat individuals affected by this still poorly understood condition.

3.1.3 Infection Curve of the Cohort Patients by SARS-CoV-2

For a portion of the cohort, we were able to obtain the date of acute SARS-CoV-2 infection through positive PCR results. However, many patients had no PCR confirmation, either because testing was not yet available at the time, was not performed or considered, was no longer reimbursed, or, in rare cases, because the patient did not recall having had an acute COVID episode despite a family infection.

Figure 3.3 presents the infection curve of the cohort. Analysis of follow-up data from 200 patients shows that case dynamics closely mirrored the major European epidemic waves.

In March 2020, more than 30 cases were recorded, corresponding to the first wave linked to the ancestral Wuhan strain. In fall 2020, the number of cases peaked at nearly 35, in parallel with the second wave and the emergence of the Alpha variant [91, 92]. Another rise was observed in fall 2021 (about 20 cases), coinciding with the Delta wave that was then dominant in Europe [93]. Finally, from December 2021 onward, cases stabilized at a low level, associated with the spread of the Omicron variant and its sublineages, which

were more transmissible but generally less severe and linked to a reduced likelihood of long COVID [94].

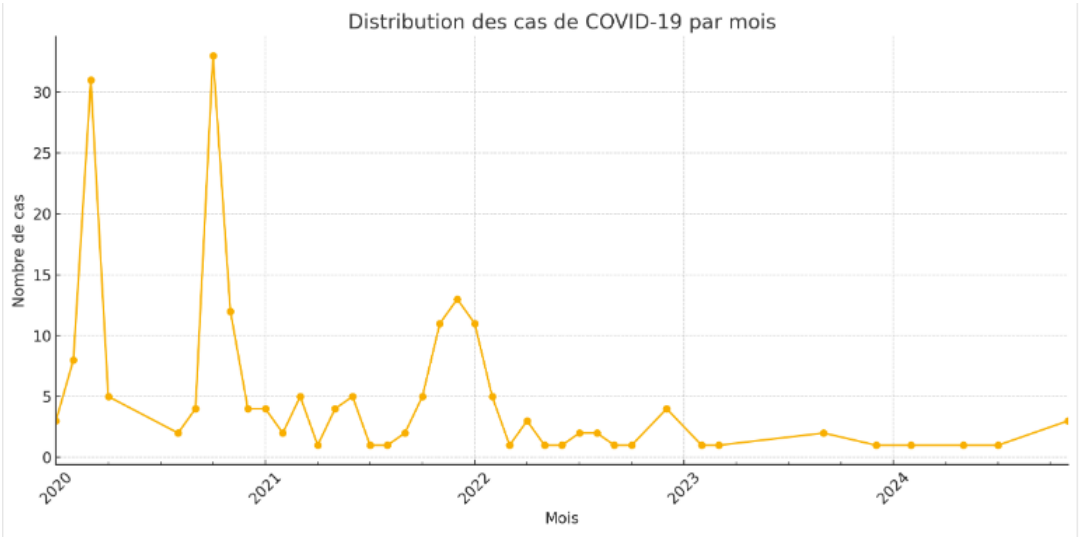


Figure 3.3 – Monthly infection curve of 200 patients clinically affected by acute COVID who subsequently developed long COVID. Consultations, Charleroi. Dr. Jamoulle and Dr. Zayane, 2021–2025.

3.2 Evaluation of the Severity and Functional Status of Long COVID Patients

By Marc Jamoulle

3.2.1 Clinical Severity Index at Cohort Entry

Clinical severity was assessed by the physician during the initial in-person consultation, using the DUSOI severity index. This index allows classification of cases according to four degrees: moderate, severe, very severe, and extreme.

The **moderate category (rated 2)** — 38 patients presented with unusual symptoms such as recurrent headaches, tinnitus, or paresthesia, but without major impact on daily life.

The **severe category (rated 3)** — 122 patients whose daily life was disrupted by multiple symptoms, especially recurrent fatigue; activities remained possible but often only part-time.

The **very severe category (rated 4)** — 154 patients who had lost the ability to lead an independent life. They were no longer professionally active, or only episodically for the most resilient, and required support in managing daily activities.

The **extreme category (rated 5)** — 2 patients with the most severe forms: one patient died following a recurrence of hematologic cancer, and the other remained hospitalized for a polymorphic debilitating condition without a definitive diagnosis.

This severity index, as estimated by the clinician, thus provides an essential benchmark for understanding multimorbidity and the trajectories observed in Long COVID.

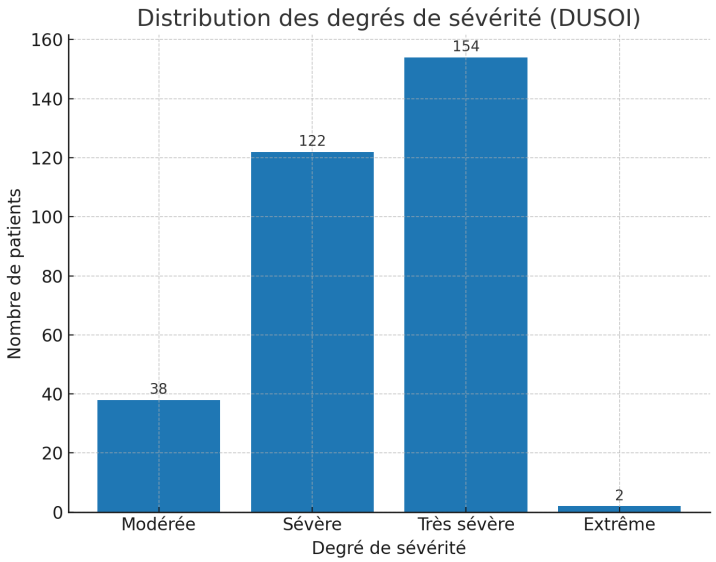


Figure 3.4 – Severity levels of the cohort according to the DUSOI. Data available for 316 patients out of a total of 337 included (as of January 15, 2025; consultations Dr. Jamoulle, 2021–2025).

3.2.2 Self-Assessment by Patients Using the COOP/WONCA Charts

As described in the Methods section, patients completed the *COOP/WONCA Charts* online using their unique identifier. This procedure enabled standardized collection of patient-reported outcomes (PROMs) while ensuring continuity and anonymity.

Functional assessment highlights a severe and generalized impairment across several key dimensions of daily life. A detailed analysis of results obtained from a sample of patients reveals a marked concentration of scores in the most severe categories, with major consequences on the ability to maintain professional, educational, or social activities. This situation raises important public health concerns, both clinically and socioeconomically.

Figures 3.5 and 3.6 show the analysis of the collected data. A predominance of scores 4 (very severe) and 5 (extremely severe) is observed across all evaluated dimensions. The weighted mean of responses per dimension ranges from 3.8 to 4.2, indicating major functional impairment.

— 81.7 % of respondents perceive themselves as being in a very severely or extremely impaired health state.

— Emotional and social dimensions show significant loss of functioning, with more than two-thirds of patients in the highest score ranges.

— Daily activities are compromised in nearly 70 % of respondents.

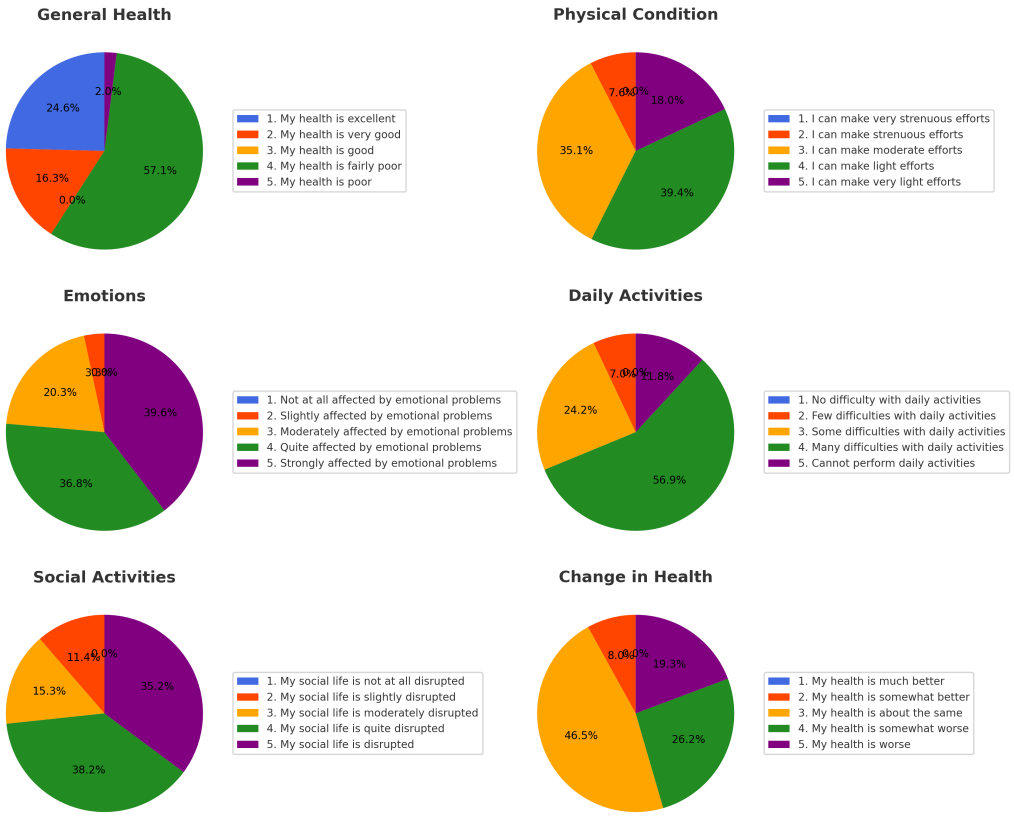


Figure 3.5 – Patients' perceptions expressed through responses to 6 COOP Charts. Scores from 1 (excellent health) to 5 (very impaired health). A patient in excellent health would have a score of 6/30. Here we show the percentage for each score. The disease severely affects patients' functional status.

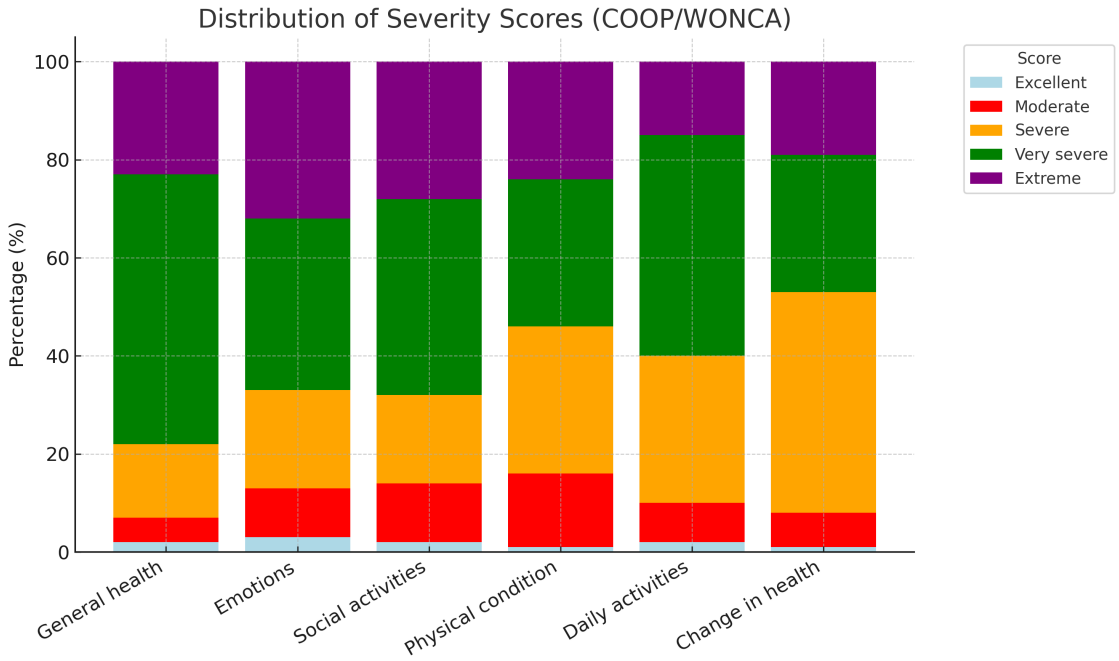


Figure 3.6 – Distribution of severity scores from the 6 COOP Charts perceived by 203 patients. We observe that health status is severely impaired, remains unchanged, or worsens. Under these conditions, patients can no longer work and schoolchildren no longer attend school.

3.2.3 A New Clinical Posture: Shared Observation

In the context of a new disease, no one knows anything—neither the patient nor the physician. The physician–patient relationship must be reinvented. Time must be taken to listen, to document, and to map the reported symptoms. The physician thus becomes a kind of Humboldt, exploring a new clinical territory in which the patient is the expert of their lived experience [1]. This type of relationship, based on reciprocity and shared expertise, fits into a clinical partnership approach [95].

This partnership requires tools to organize and cross-reference knowledge: on the one hand, knowledge derived from patients' subjective experiences; on the other, knowledge from the scientific literature and the collective expertise of caregivers.

Regarding patients' experiences, tools such as patient texts (personal records, lived stories, emails), the electronic medical record, automatic transcription of clinical interviews, and symptom annotation using the HPO ontology are mobilized.

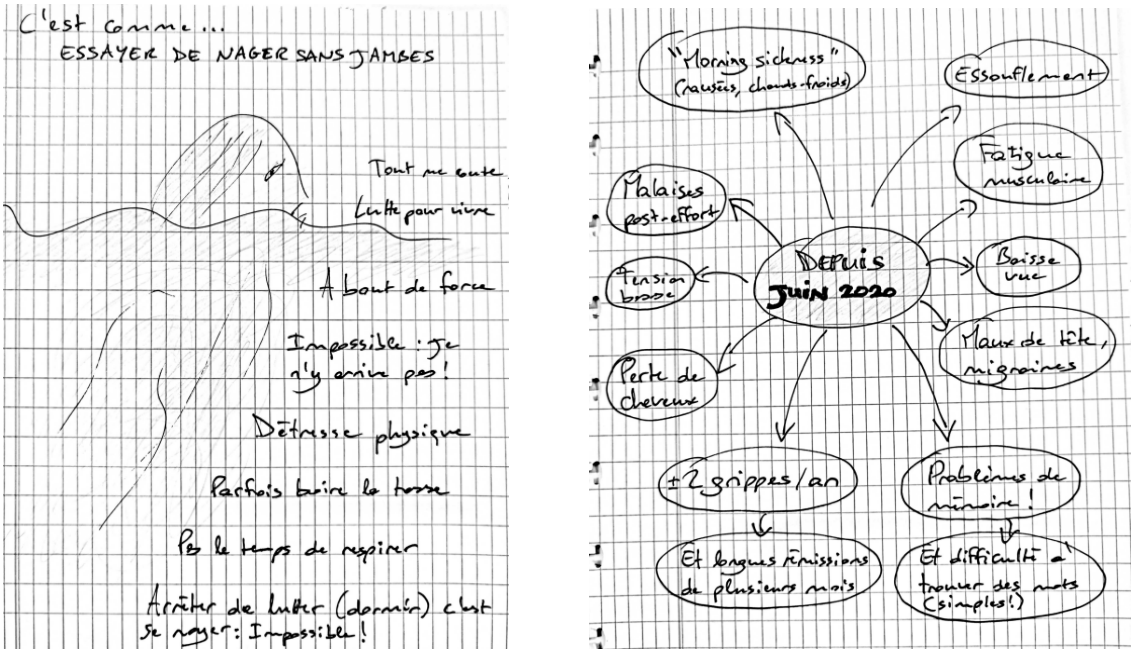


Figure 3.7 – Patient as expert of their disease. Drawing and notes brought to consultation. Reproduced with the patient's permission (M. Jamoulle, 2024).

An example of such material is shown in Figure 3.7. Two drawings brought by the patient illustrate her lived experience of the illness. In the first, she describes (in French) her condition with powerful metaphors: *It is like trying to swim without legs. Everything eats away at me. Struggling to live. Exhausted. Impossible! I can't do it! Physical distress. Sometimes swallowing water. No time to breathe. Stop struggling! Sleep! It feels like drowning.*

The second drawing takes the form of a circular graph, starting from *since June 2020* and unfolding clockwise. The patient maps a cascade of symptoms: *shortness of breath, muscle fatigue, visual decline, headaches, migraine, memory problems, a question mark, word-finding difficulties (simple words!), recurrent flu-like episodes, long remissions of several months, followed by hair loss, low blood pressure, post-exertional malaise, and what she calls *"morning sickness"* (nausea, alternating hot and cold).* Together, these drawings provide a striking narrative of her fluctuating but persistent illness experience.

The consequences are economic (income loss, financial hardship) but also social and

familial: isolation, relational tensions, and sometimes complete family disorganization. Cases of economic and psychological distress are regularly reported in this context.

The following observation (See Figure 3.8) concerns an adolescent with Long-Covid, whose father, an IT specialist, carefully documented the intensity and significance of her symptoms from the onset of the illness. The resulting record offers a rare longitudinal view of the disease's evolution. The graph shows how some symptoms persist continuously while others appear in a remitting pattern, creating a highly complex picture. Such complexity is difficult to interpret, both for physicians who may be unfamiliar with this emerging condition and for patients and families confronted with an illness largely absent from the traditional culture of health care.

These data call for formal recognition of the functional disability induced by Long COVID and for adaptation of social, educational, and professional support systems. The absence of objective biomarkers should not obscure the lived reality of patients, which functional assessment tools such as *COOP/WONCA* help to rigorously document.

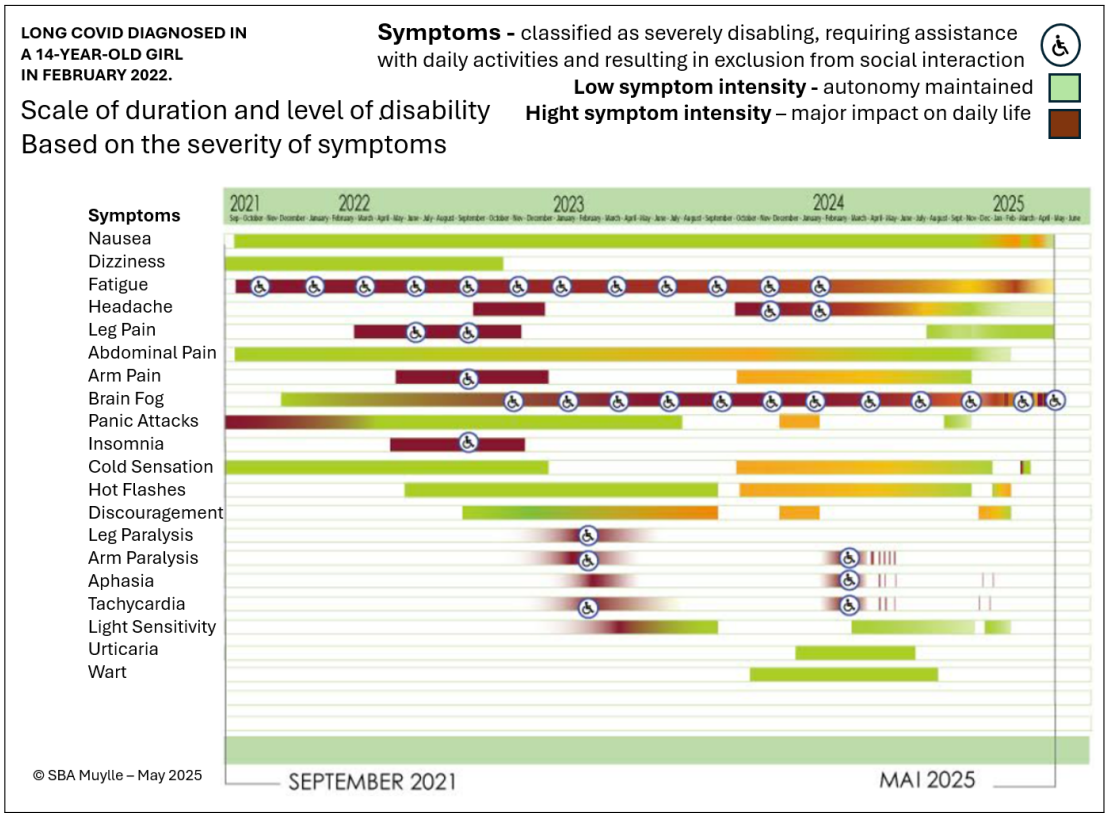


Figure 3.8 – Symptom evolution in an adolescent, first infected with COVID-19 in 2022 at age 14. Symptoms in green are least disabling, in burgundy most disabling. The PMR symbol indicates severe disability preventing social life. Document provided by the patient, with permission.

3.3 Long COVID Symptom Analysis

Symptom extraction from clinical texts

Large Language Models (LLMs) can automatically extract relevant symptoms from unstructured clinical notes, enabling the construction of detailed, personalized symptom profiles for each patient [96, 97]. This capability facilitates the identification of recurrent patterns associated with Long COVID, even when they do not correspond to classical nosological entities.

LLMs can contribute to medical decision-making by suggesting diagnostic hypotheses based on identified symptom patterns, thereby providing valuable support to health professionals in managing complex conditions such as Long COVID .

In this example, the email that the patient wrote to describe her health status is reproduced with the patient's explicit consent. The transcription of this exchange made it possible, thanks to analysis by a Large Language Model (LLM), to identify and encode the symptoms according to the descriptors of the Human Phenotype Ontology (HPO) as explained in Methods (see 2.3.4. The overall clinical picture in Table 3.1 coherently suggests a post-viral syndrome.

Email received from a patient, MJ. Consultations, September 2024

The situation was really catastrophic between September 2023 and February 2024. I spent more than 70 % of that period in bed, unable to work or properly care for my children. Then, in March, I suddenly felt much better. I had moved, and I associated my improvement with that change. I felt so well that I resumed work at 40 % capacity on July 1, very happy. But at the end of August, I collapsed again after catching COVID. I stayed in bed until November, working only 20 %. November was excellent, but things worsened again after a slight cold last week (self-tests negative).
When I crash, it's almost always the same symptoms: overwhelming fatigue, a burning sensation in the brain, the feeling that molten lead is flowing through my veins, pain in my hands and feet, memory and speech problems, difficulty moving around, occasional hair loss, chest pain near the heart and, since September, difficulty breathing. But there are times when I feel perfectly fine, and I make the most of it :) Overall, things are improving, slowly but surely. I was first infected in October 2020.

Table 3.1 – Distribution of symptoms by clinical categories and their HPO code identified by ChatGPT in the patient's email described above.

General symptoms	**Dermatological symptoms**
Fatigue (HP:0012378) [overwhelming fatigue]	Alopecia (HP:0001596) [occasional hair loss]
Neurological symptoms	**Cardiovascular symptoms**
Burning sensation (HP:0033217) [burning sensation in the brain]	Chest pain (HP:0100749) [chest pain near the heart]
Memory impairment (HP:0002354) [memory problems]	**Respiratory symptoms**
Speech impairment (HP:0002167) [speech problems]	Dyspnea (HP:0002094) [difficulty breathing]
Gait disturbance (HP:0001288) [difficulty moving around]	
Musculoskeletal symptoms	
Pain in limb (HP:0009763) [pain in my hands and feet]	

3.3.1 Symptom Mapping

By linking extracted symptoms to a structured terminology such as the *Human Phenotype Ontology* (HPO), the LLM produces coherent documentation and enables systematic analysis, facilitating the identification of symptom clusters typical of Long COVID. Phenotypic labels generated by the language model (LLM) from clinical descriptions contained in texts, emails, personal narratives, or clinical interviews of **307** patients were aggregated.

Tables 3.2 and 3.3 illustrate an example of structured information resulting from the analysis of a patient record. This concerns a young woman, aged 26 at the time of her first SARS-CoV-2 infection in October 2020, long known in general practice. Her medical history begins with minor thalassemia, coded in January 2016 (B78), followed in 2016 by an episode of kidney stones (U95). In 2018, exercise-induced asthma was diagnosed (R96). In 2020, she delivered her first child (W90), a few months before a first COVID-19 infection (A77). A second infection was documented in July 2021. The diagnosis of post-COVID syndrome (Long COVID) was considered in February 2023 (MGA.xxx), followed by a new infectious episode in February 2024. She is currently pregnant with her second child which, in the context of her post-COVID status, justifies classification as a high-risk pregnancy (W94). All medical events are coded according to the ICPC-2 classification (Table 3.2).

List of the patient's health problems
U95 – Kidney stones – 01/2016
B78 – Minor thalassemia – 08/2016
R96 – Exercise-induced asthma – 06/2018
W90 – Normal delivery – 06/2020
A77 – COVID-19 infection – 07/2020
A77 – COVID-19 infection – 07/2021
MGA.xxx – Long COVID – 02/2023
A77 – COVID-19 infection – 02/2024
W94 – Confirmed pregnancy in LC – 03/2025

Table 3.2 – Patient's medical problem list classified in ICPC-2. Three acute COVID episodes, including one after the diagnosis of Long COVID.

Table 3.3 presents the same patient phenotypic label (as of February 2023). Each statement begins with the standardized English HPO term followed by its alphanumeric identifier; the patient's verbatim enabling semantic alignment is shown in brackets. While the semantic matches proposed by the language model are generally pertinent, the HPO identifiers may not always be exact. Validation of automatic matches is addressed in a verification protocol presented in Chapter **??**.

The aggregation of **307** phenotypic vignettes from our cohort yields a structured database containing more than 350 distinct phenotypes, encoded using HPO descriptors. This structuring enables quantitative analysis of symptom frequency. Figure 3.9 presents the 50 most frequently observed symptoms in the sample.

Analysis of these data shows that the clinical picture of Long COVID is dominated by memory disorders. The next most frequently reported symptoms include headaches, anomic aphasia (word-finding difficulty), concentration disorders, and dyspnea. This symptom hierarchy is partly dependent on the observer's interpretation: all 307 vignettes were constructed by the same practitioner, with four years of experience supporting and documenting Long COVID patients.

Patient's phenotypic label (symptoms coded in HPO)
Severe fatigue (HPO:0012378) [Extreme, overwhelming fatigue, inability to carry out daily tasks]; Non-restorative sleep (HPO:0012459) [Feeling of heaviness on waking, non-restorative]; Reduced multitasking ability (HPO:0012442) [Inability to be multitasking as before]; Impaired attention (HPO:0000739) [Difficulties with concentration and attention]; Memory impairment (HPO:0002354) [Memory loss, frequent forgetfulness]; Reduced ability to follow conversations (HPO:0001338) [Inability to follow a conversation or a movie]; Word-finding difficulties (HPO:0002451) [Difficulty finding words]; Sleep disturbance (HPO:0031046) [Difficulty sleeping despite intense fatigue]; Restless legs (HPO:0002375) [Nighttime restlessness, frequent leg movements]; Dysregulated thermoregulation during sleep (HPO:0032228) [Alternating hot and cold sensations, without taking temperature]; Reduced appetite (HPO:0004396) [Loss of appetite, reduced desire to eat]; Weight loss (HPO:0001824) [Apparent weight loss]; Paresthesia of the hands (HPO:0003401) [Tingling and pins-and-needles in the hands]; Muscle cramps (HPO:0003394) [Frequent muscle cramps, especially in hands, arms, and jaw]; Orthostatic dizziness (HPO:0002321) [Dizziness when standing, often related to postural changes]; Reduced sense of smell (HPO:0002103) [Occasional reduction in smell]; Reduced sense of taste (HPO:0002165) [Occasional reduction in taste]; Tinnitus (HPO:0000360) [Frequent ringing in the ears]; Dyspnea (HPO:0002090) [Shortness of breath even without significant effort]; Decreased physical activity tolerance (HPO:0004322) [Inability to engage in physical activities]; Palpitations (HPO:0001627) [Occasional palpitations associated with dizziness]; Decreased sexual activity (HPO:0002984) [Reduced spontaneity in sexuality due to fatigue]

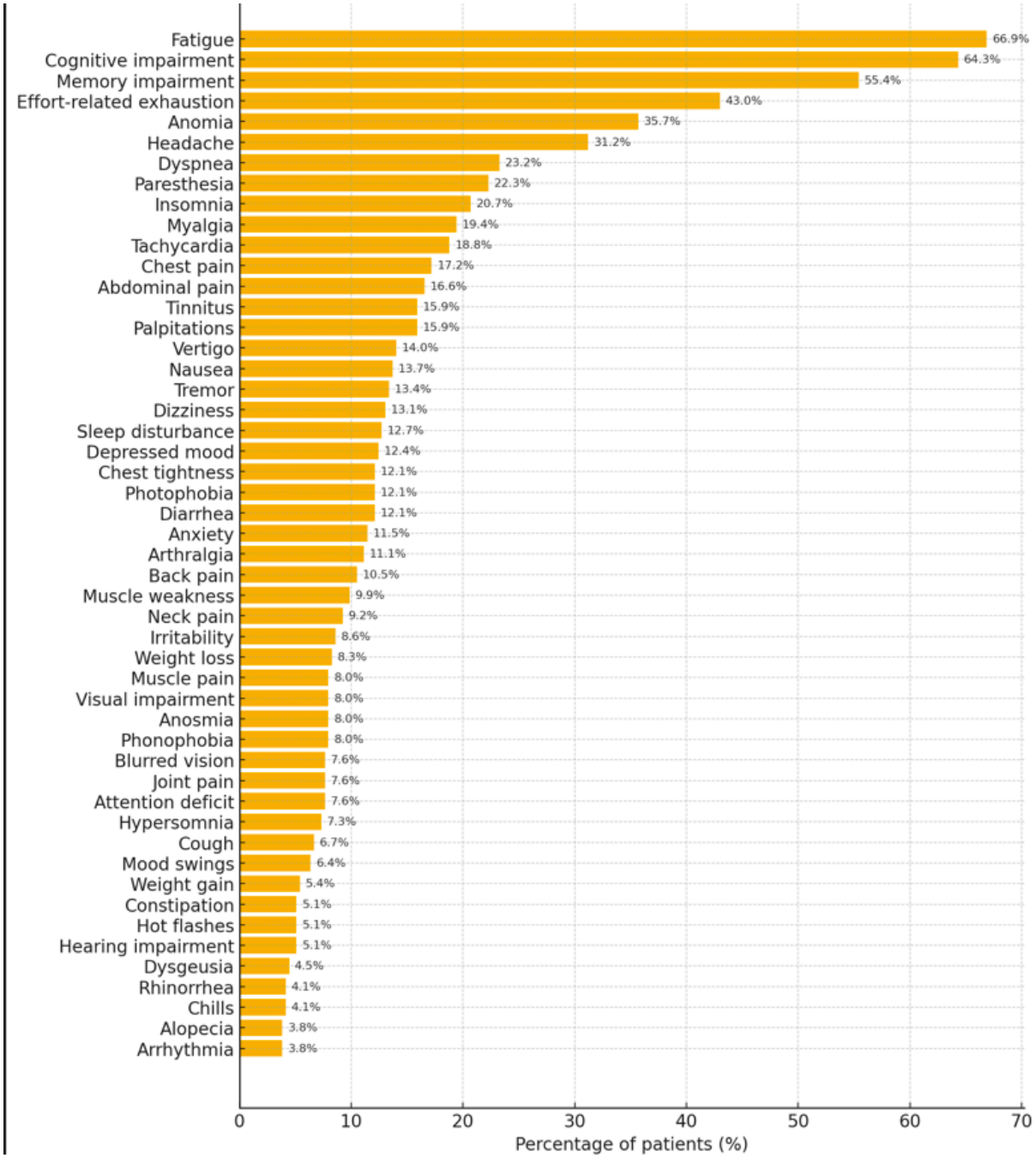
Table 3.3 – Long COVID symptoms identified and encoded according to the Human Phenotype Ontology (HPO). HPO term; HPO code; patient verbatim. Phenotypes recorded in the patient from Table 3.2. (M. Jamoulle, consultations, 2024).

The overall distribution broadly aligns with trends reported in the existing epidemiological literature on Long COVID [98]. However, the resulting symptomatic profile does not overlap with any other known nosological entity. Consequently, organizing symptoms encoded with HPO can be considered a **terminological biomarker**: a reproducible linguistic/semantic feature extracted from patient narratives that enables standardized mapping of symptoms onto controlled vocabularies—reflecting the clinical specificity of a still poorly characterized syndrome.

3.3.2 Distribution of Long COVID symptoms in the cohort

Semantic analysis of interviews and medical records, conducted according to the method described, has to date made it possible to identify sets of symptoms in 307 patients. Figure 2.8 illustrates this coding process, while Figure 3.9 shows the distribution of the **50 main symptoms** reported by the cohort. It should be noted that these symptoms are not grouped by organ systems, but follow the patients' verbatim, thus more faithfully reflecting their lived experience.

Figure 3.9 – Distribution of the 50 main symptoms expressed in HPO terms among 307 patients seen in general practice in Belgium as of July 1, 2025 (Marc Jamoulle. Consultations, 2021–2025).)



The observed distribution is clinically significant. The recurrent association of fatigue, cognitive disorders (including memory impairment), exertional exhaustion, speech impairment, headaches, dyspnea, and paresthesias does not correspond to any classic, well-defined pathological picture. However, this grouping of symptoms fits coherently within clinical descriptions of post-COVID syndrome. Even for an experienced clinician, the multi-system involvement thus highlighted can be disconcerting, especially since each patient presents with a specific symptomatic configuration. Some individuals express only a few manifestations of Long COVID, which further contributes to the complexity of diagnosis. As shown in Figure 3.8, symptoms also fluctuate over time and are not always concomitant, making diagnosis particularly challenging in the absence of reliable biomarkers.

One major finding emerges from the interviews: the vast majority of patients report a clear deterioration in their health after the acute episode of COVID-19. The distinction between a "before" and "after" infection is a recurring theme, with patients frequently expressing the feeling of never having regained their initial state of health. This subjective element, absent from statistical tables, nonetheless constitutes a fundamental datum of clinical narratives.

Finally, it appears that acute infection affects both people previously in excellent health and patients with multiple comorbidities. In the latter, differentiating between effects related to preexisting morbidity and those attributable to Long COVID is particularly challenging. This difficulty is especially marked in patients already presenting an autoimmune disease, such as lupus or rheumatoid arthritis, or a chronic condition like diabetes or certain urological disorders (for example urinary retention). The manifestations of these conditions can indeed overlap with those of Long COVID, making etiological attribution of symptoms more complex.

In plain language

Understanding Long COVID: a clinical investigation in family medicine

Understanding Long COVID: a family medicine perspective
Family doctors began to notice that some patients, who had been healthy before, were experiencing long-lasting health problems after COVID-19. These people often reported extreme tiredness, memory or concentration troubles, body pain, or shortness of breath — even months after the initial infection.
To make sense of this, doctors listened closely to their patients, wrote down all their symptoms, and searched for explanations in medical research. Step by step, a new condition came into focus: Long COVID.
Researchers then used a tool called the Human Phenotype Ontology (HPO), which helps classify symptoms in a clear and structured way. Thanks to this, they realized that Long COVID can affect many systems in the body — physical, mental, and emotional — with a strong impact on daily life.
More recently, scientists have also turned to artificial intelligence, such as ChatGPT, to analyze patients' stories and highlight common patterns. This helps track how symptoms change over time and adapt care accordingly.
In this process, patients play an active role: their personal experience and the way they describe it are key to better understanding this still poorly known condition. The role of the family doctor is to listen, document, and connect these personal stories with scientific knowledge.

3.4 Managing Symptoms and Supporting Patients

3.4.1 The Therapeutic Relationship: A Foundational Element of Care in the Context of Long COVID

The care of a patient begins with the clinical encounter. Active and attentive listening, provided within an atmosphere of empathy, constitutes the basis of any credible medical practice. In the context of Long COVID, where diagnostic and therapeutic reference points remain uncertain, the act of naming the condition and acknowledging the patient's lived experience already represents a significant therapeutic intervention. Such recognition validates suffering, mitigates isolation, and initiates a process of recovery.

The subsequent step involves the establishment of a partnership grounded in trust, sustained by the transparent communication of uncertainties and by mutual commitment to the exploration of treatment options. In this framework, the physician assumes the role of a companion and attentive guide, rather than solely that of a prescriber, within a therapeutic alliance that relies on collective reasoning, continuous adaptation, and mutual respect.

Given that the consequences of Long COVID are frequently socially and economically debilitating, the therapeutic approach must also extend to the domain of social advocacy on behalf of patients. Assisting individuals in obtaining recognition of their condition from insurance agencies, accessing entitlements, and securing protection in the face of administrative uncertainty constitutes an integral component of comprehensive therapeutic support.

Social support resources may be mobilized to reinforce this comprehensive approach. In Wallonia, the nonprofit organization *Le Ressort* ("The Support Network"), supported by the *Agence Wallonne pour une Vie de Qualité* (AViQ, "Walloon Agency for Quality of Life"), plays a central role in the care of individuals with acquired brain injury, including patients with Long COVID who present with persistent cognitive impairment. Their interventions are essential in strengthening resilience and promoting reintegration into social, family, and professional life. Thus, medical care extends beyond the prescription of treatment: it encompasses recognition, support, advocacy, and connection.

3.4.2 Multiple Symptomatic Treatments in a Disorganized Therapeutic Landscape

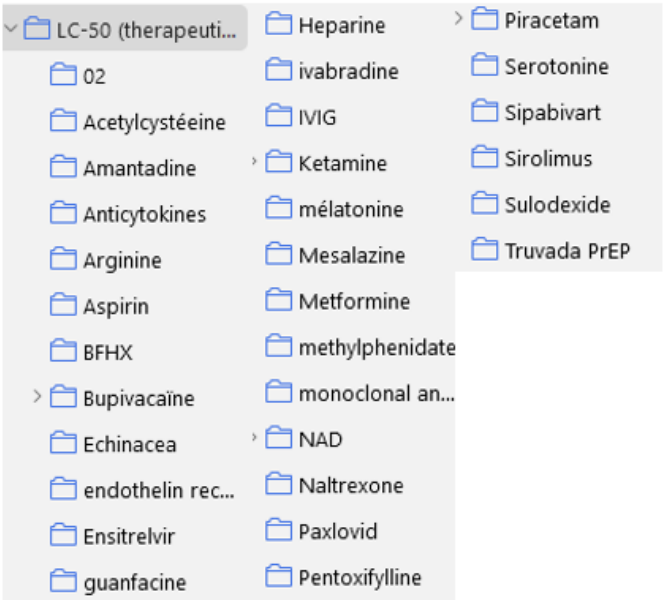
In the absence of a validated etiological treatment for Long COVID, patient care relies on a mosaic of pharmacological and non-pharmacological measures, tailored to the complexity and variability of symptoms. The goal is to alleviate suffering, support resilience, and—whenever possible—restore impaired functional capacities.

The intention here is not to list in detail the many prescriptions frequently used—analgesics, antimigraine drugs, mood regulators, or anxiolytics—but to emphasize their indispensable role in addressing chronic pain, disabling headaches, anxiety, or that quiet sadness described by many as a feeling of being *"in mourning for oneself."* Such treatments must be personalized, reassessed over time, and integrated within a therapeutic relationship grounded in attentive listening.

Among non-drug measures, several approaches have been explored—hyperbaric oxygen therapy, transcutaneous vagus nerve stimulation, or ketamine infusions in specialized settings. Each shows variable and still uncertain results in the literature, with off-label indications. In Belgium, the national insurer has established a theoretically accessible

care package that includes neuropsychology, physical therapy, dietetics, and occupational therapy.

Figure 3.10 – Ranked literature review of substances and therapeutic protocols explored in Long COVID, most often at patients' request. Source: Long COVID Open Library (Zotero).



Yet this initiative is hampered by major limitations: information about available services is scarce, the list of providers is not public, access is conditional and time-limited, the number of trained professionals is insufficient, and no coordinated training has been provided to primary care. Most professionals therefore act in isolation, guided by personal means and intuition, without a shared framework. By the fifth year of the pandemic, and despite international advances in neuropsychology [99] and functional rehabilitation [100], Belgium still lacks national guidelines. This absence of a coordinated vision for both caregivers and patients is deeply concerning.

The distress of Long COVID patients is immense. Confronted with persistent symptoms, fragmented care, and the lack of standardized protocols, many turn to social networks in search of comparable experiences, testimonies, or alternative solutions. This reliance on online information reflects a legitimate quest for understanding and relief, but also exposes patients to a flood of unvalidated proposals—often ineffective, sometimes harmful. In this context, it is essential to safeguard patients by providing reliable, accessible, and regularly updated information grounded in verified data. This means not only correcting misconceptions or unfounded narratives, but also offering cautious and transparent therapeutic orientations, proportionate to current scientific knowledge. Such support presupposes substantial research work: continuous literature review, critical appraisal, expert consultation, and systematic cross-checking of sources.

3.4.3 Sipavibart: an innovative approach in the context of Long COVID, for targeted use

Sipavibart is a recombinant human monoclonal antibody (IgG1) targeting the receptor-binding domain of the SARS-CoV-2 Spike protein. By blocking interaction with the ACE2 receptor, it provides transient passive immunization that may be beneficial both in prevention and in contexts of viral persistence. Its mechanism, akin to passive vaccination, differs, however, by the absence of sustained stimulation of the immune response [101].

Within a compassionate-use protocol coordinated by Dr. Gilles Force, infectious disease specialist at the Franco-British Hospital in Paris, three French patients from our cohort with severe Long COVID and repeated reinfections received a Sipavibart injection. This approach was accompanied by rigorous follow-up, based both on patients' daily self-assessments of symptoms (via "heatmap"-type tables filled in by the patients) and on a transcriptomic analysis protocol (conducted by Prof. Johan van Weyenbergh), with pre- and post-injection sampling (time 0 and at three months).

Figure 3.11 – Sipavibart clinical trial. The patient lists her symptoms and rates them from 0 (absent—green) to 6 (very severe—red). Sipavibart injection in December 2024 (Dr. Gilles Force, Franco-British Hospital, Paris). The patient assigns a daily score to her symptoms (Google Sheet shared with her family physician, who follows the case on a smartphone). In April, a remarkable improvement is seen, but exertion remains impossible (score 6). Blood samples for transcriptomic analysis are taken before and at the third month of treatment.

MGA054	TEST	20/12/2024	21/12/2024	22/12/2024	23/12/2024	24/12/2024	25/12/2024	29/03/2025	30/03/2025	31/03/2025	01/04/2025
Jour		8	9	10	11	12	13	107	108	109	110
Malaise post-effort	4	3	1	1	4	6	2	0	0	1	1
Fatigue	4	4	2	2	5	6	3	1	0	1	1
Essoufflement	4	3	3	2	3	3	3	0	0	0	0
Nausées	2	1	0	1	0	5	1	0	0	0	0
Douleur nuque	3	2	5	5	5	4	3	1	1	0	0
Difficultés à rester debout	3	3	1	1	1	2	3	0	0	0	0
Tachycardie / Arrhythmie	3	2	2	1	1	1	1	1	1	1	1
Dyspnée / Hyperventilation	4	5	5	4	4	4	5	0	0	0	0
Insomnie	5	6	5	0	1	3	3	0	0	0	1
Brouillard cérébral	2	1	1	1	1	2	1	0	0	0	0
Maux de tête	4	3	1	2	0	0	2	0	0	0	0
Problèmes de mémoire	2	1	1	0	0	0	0	0	0	1	1
Problèmes de langage	1	1	1	0	0	0	0	0	0	0	0
Secheresse occulaire	1	2	2	1	2	1	1	1	1	1	1
Acouphènes	0	1	0	0	0	0	0	1	1	1	1
Total symptoms	42	38	30	21	27	37	28	5	4	6	7
Degré d'activité physique	2	3	5	5	6	5	5	5	4	5	6

The clinical results observed are very encouraging: after a transient phase of symptom worsening (lasting about 3 to 4 weeks), the three patients experienced a clear and prolonged improvement, marked particularly by the disappearance of post-exertional "crashes," a particularly disabling symptom of Long COVID. The positive effects appear stabilized at three months, without major relapses, which represents a turning point after several years of debilitating chronic evolution. The patients involved regard this intervention as a promising therapeutic experience.

However, several important limitations must be taken into account. The effectiveness of *Sipavibart* depends heavily on the circulating variant. While it remains active against certain strains (such as JN.1.1), it loses its neutralizing capacity against recent variants such as KP.1.1, LB.1, or KP3.3. Widespread use could favor selective pressure on the virus and accelerate the emergence of resistant mutations, as observed with other monoclonal antibodies. Critical analysis of a clinical trial published in 2025 in *The Lancet Infectious Diseases* (SUPERNOVA, conducted in immunocompromised patients) showed that the rapid emergence of the Phe456Leu mutation rendered Sipavibart ineffective in more than 90 % of the cases studied, even before its wide availability [102, 103].

In short, the experience conducted with these three patients opens important prospects for personalized care in Long COVID, but calls for caution in generalizing the use of Sipavibart, given the rapid evolution of SARS-CoV-2 variants and the delicate balance between individual benefit and collective risk.

3.4.4 Paxlovid: supervised use of an antiviral in patients with Long COVID

Continuing the method of collaborative follow-up by symptomatic heatmap described above, and in response to persistent requests from certain patients, an exploratory protocol was implemented in 2023 concerning the supervised use of Paxlovid (nirmatrelvir/ritonavir) in individuals with Long COVID. The objective was to test the hypothesis of active viral persistence in these patients by observing the effect of antiviral therapy on chronic symptomatology.

In total, 17 selected patients received Paxlovid for an extended duration of 15 days, with rigorous clinical follow-up including: daily symptom evaluation via a personalized heatmap on Google Sheets (see Figure 3.12), a parallel logbook, and transcriptomic analyses before and after treatment, carried out in collaboration with Johan van Weyenbergh's laboratory (KU Leuven).

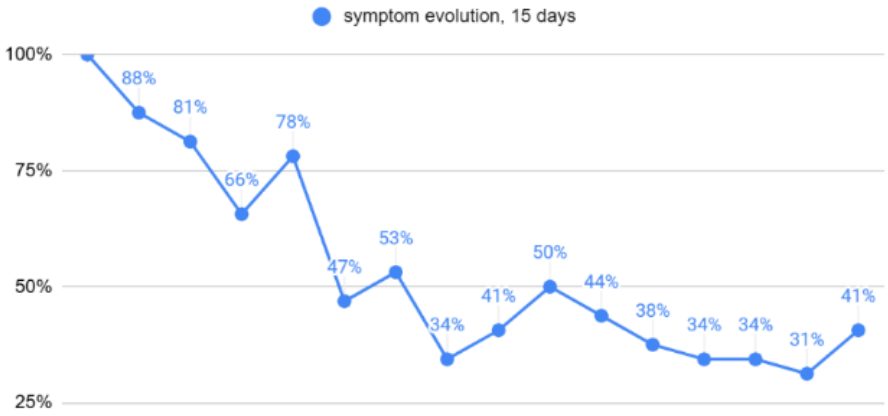
In four patients, an improvement as spectacular as it was unexpected was observed within the week following administration, with a rapid and marked decrease in symptoms. However, this improvement was short-lived: after three weeks, the symptomatology reappeared in an almost identical manner, suggesting possible viral reactivation after treatment cessation or inefficacy of the drug on persistent reservoirs. The patients who experienced this temporary relief still recall it vividly two years later.

This variability in response, combined with the high cost of treatment and the absence of therapeutic predictability, led to the decision not to extend the experience on a larger scale. Only one patient discontinued the course prematurely due to digestive intolerance, while no serious adverse events were reported in the other participants.

Despite its partial clinical failure, this initiative led to notable progress in basic research: biological samples collected before and after treatment were stored in a biobank and already serve as the basis for molecular biology investigations. They contribute notably to elucidating the mechanisms of SARS-CoV-2 persistence and the associated immune signatures.

Figure 3.12 – One of the 4 positive responses among 17 participants. Daily assessment was performed by the patient herself, who assigned a score from 0 (symptom absent—green) to 6 (very severe symptom—red) to each listed symptom. Paxlovid (nirmatrelvir/ritonavir) treatment began in mid-January 2024. On February 3, the date the twice-daily 15-day course ended, a clear decrease in the overall intensity of symptoms was recorded, with, however, persistence of fatigue and sleep disturbances. In the following weeks, the beneficial effect faded, with a progressive resurgence of symptoms. (Heatmap for LC symptoms, © mj & el).

MGA_124 (adapter les dates) (retour au journalier)	TEST ce jour 19/01/2024	1/2/2024	2/2/2024	3/2/2024
Jour		13	14	15
Fatigue extrême	4	6	5	5
Fatigue oculaire	0	0	0	0
Rhinorhée	5	0	0	0
Mal de gorge	5	0	0	0
Toux	4	0	0	0
Insomnie	6	6	6	6
Sensation vertigineuse	3	2	2	3
Acouphène	1	2	1	2
Inappétence	4	1	1	2
Diarhée	0	0	0	0
total symptomes	32	11	10	13



3.5 Pediatric Cohort: Narratives, Symptom Patterns, and Functional Impairment

By Marc Jamoulle & Serhan Soylu

The pediatric subgroup in our series comprised ten children, aged 7 to 16 years, representing about 3% of the larger general practice cohort of 307 long COVID patients in Charleroi, Belgium. Seven of the ten were girls, consistent with the overall female predominance in the broader cohort (67% as of July 2025).

3.5.1 Patient Narratives and Lived Experience

To illustrate lived experience, Table 3.4 presents selected quotes from interviews with children and their caregivers. These narratives highlight pervasive functional disruption, emotional strain, and social withdrawal.

Table 3.4 – Selected child and caregiver quotes illustrating functional impact in pediatric long COVID (2022–2025).

Speaker	**Quote**
Boy, 12	*I want to go to school, but my body won't let me. I wake up already tired. When I try to run a little, everything hurts and I have to go to sleep.*
Girl, 13	*I used to dance three times a week. Now, just getting up and washing my hair takes me all morning.*
Mother of boy, 10	*He's changed. He doesn't play with his friends anymore, he stays in his room, he doesn't want to go out. He says his stomach hurts, his head hurts, and that he hears strange noises in his head.*

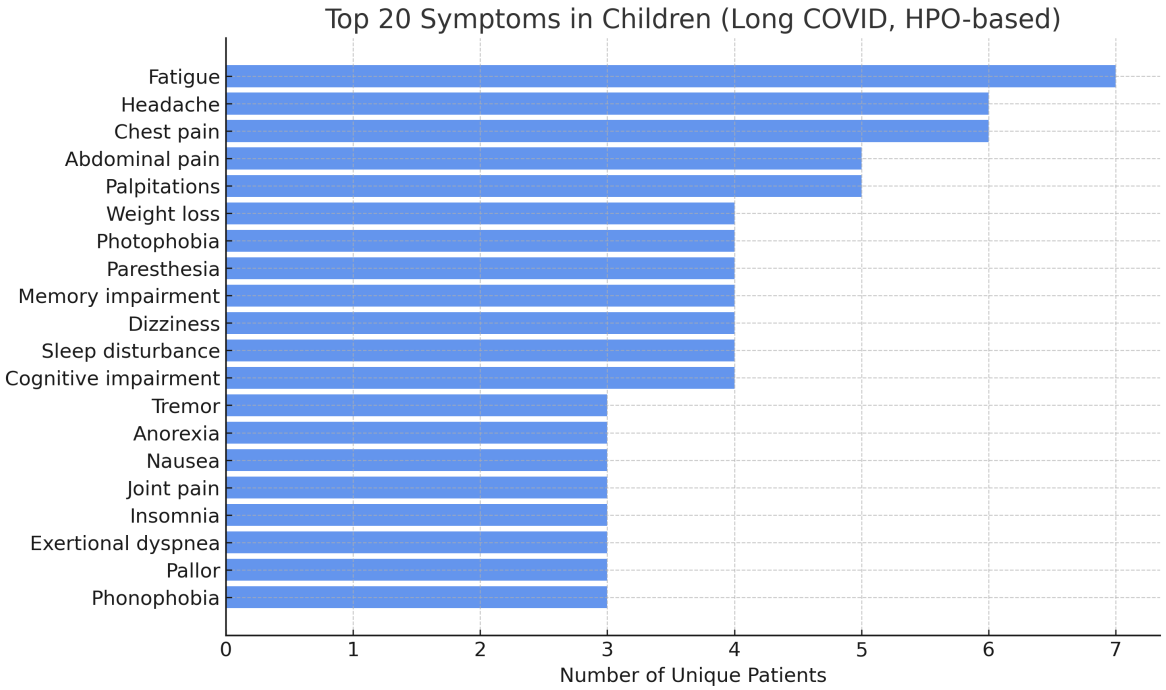
Table 3.5 – Case illustration: 11-year-old boy with post-COVID symptoms since October 2021. Withdrawn from school, previously athletic and skilled at strategic video games. Consultation by M. Jamoulle, June 2025. HPO codes are clickable links to PURLs.

Symptom	**HPO Code (PURL)**	**Child's Wording**
Chest pain	HP:0100749	"It really hurts in my sternum."
Palpitations	HP:0001962	"My heart beats faster and faster."
Syncope	HP:0001279	"I realize I fainted."
Cognitive fluctuation	HP:0033630	"Sometimes I say 1+1=3; next day it's fine."
Fatigability	HP:0003388	"I'm too tired so I stop."
Post-exertional fatigue	HP:0009020	"After I play, I have to lie down."
...	...	...

3.5.2 Symptom Patterns via HPO Annotation

All ten children presented complex, multisystem, progressively evolving symptoms. As shown in Figure 3.13, the most commonly reported complaints were fatigue, headache, and chest pain, alongside a broader constellation typical of long COVID.

Figure 3.13 – Top 20 HPO-coded symptoms in 10 children with long COVID seen in general practice (2024–2025).



The Human Phenotype Ontology (HPO) enabled real-time translation of free-form narratives into structured symptom profiles. As illustrated in Table 3.5, LLM-assisted semantic extraction converted fragmented or vague expressions into a consistent vocabulary available at the point of care. This structured representation often validated the child's story and helped strengthen therapeutic alliance. Table 3.6 shows expressions describing fatigue and sleep disturbance.

Table 3.6 – Selected expressions related to fatigue and sleep, as reported by children or caregivers (2022–2025).

"I'm tired all the time."
"I used to do sports—now I can't even stay on my feet."
"She spends all her time sleeping in class."
"I sleep, but I still wake up tired."
"I can sleep for three days straight... or not at all for three days."
"You sleep a lot. How much? 19 hours a day."

Across the sample we mapped **233 individual annotations** to HPO, corresponding to **128 distinct symptom concepts**. This redundancy reflects recurrence across patients while highlighting clinical heterogeneity. The complete set of HPO tables is provided in Annex **??**.

3.5.3 Functional Impairment and Daily Life Impact

Beyond symptoms, functional status was severely impaired. Consultations required advance preparation: review of the child's digital health record, analysis of ComPaRe and COOP/WONCA questionnaires, and integration of parental observations. Each interview lasted over 45 minutes, with a focus on daily function and emotional or cognitive

fluctuations.

COOP/WONCA charts consistently revealed severe to extreme limitations in health perception, physical activity, daily functioning, emotional well-being, and social participation (Figure 3.14).

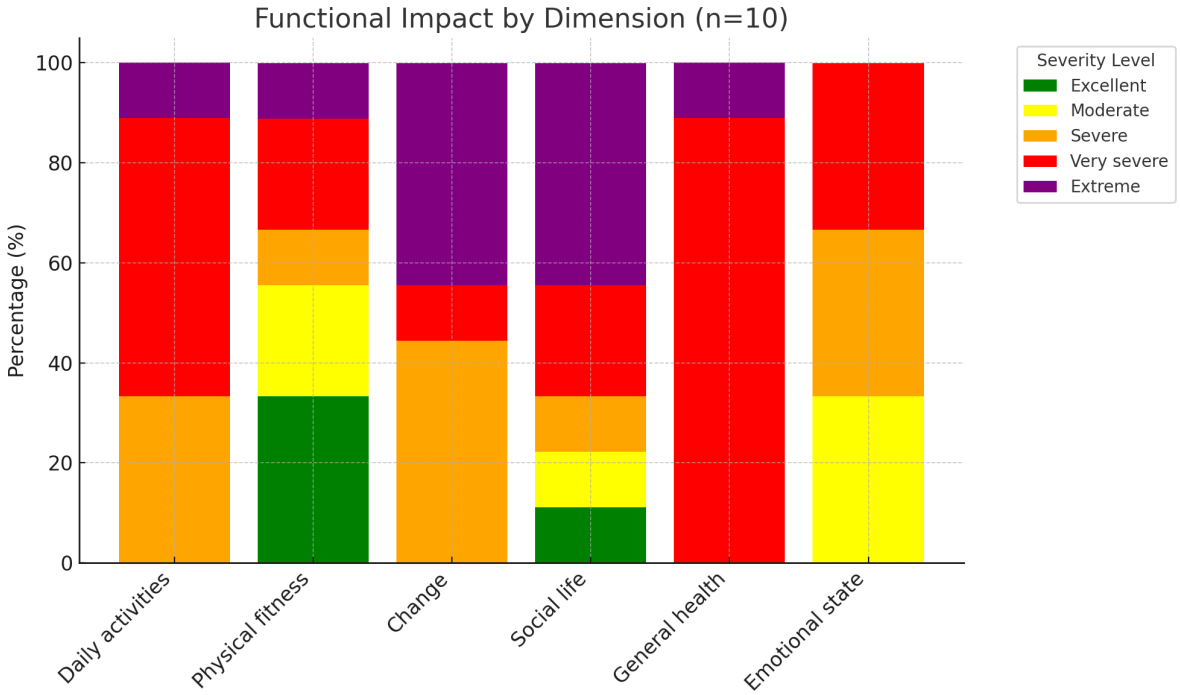


Figure 3.14 – Functional status in 10 children with long COVID, using COOP/WONCA Charts. Orange, red, and purple represent severe, very severe, and extreme limitations.

School absenteeism was universal, with several children missing months of education. Sports and peer activities had ceased in nearly all cases. Parents frequently reported exhaustion and frustration linked to diagnostic uncertainty, medical dismissal, and the invisibility of their child's condition.

Together, these results highlight the clinical, functional, and emotional burden of pediatric long COVID. They also illustrate how a narrative-informed, semantically structured, and functionally grounded protocol can clarify complex cases and improve communication between patients, families, and clinicians.

3.6 Role of Innate and Adaptive Immunity in Viral and Post-viral Inflammatory Conditions: Toward Precision Medicine

by Johan Van Weyenbergh, senior researcher in viral immunology, specializing in the study of host–pathogen interactions, inflammatory responses, and transcriptomics applied to infectious diseases. (KU Leuven – Rega Institute for Medical Research, Laboratory of Clinical and Epidemiological Virology, Department of Microbiology, Immunology and Transplantation)

While classical cell biology has enabled many advances in understanding the fundamental mechanisms of life, it shows certain limits when it comes to characterizing the complex aggression exerted by SARS-CoV-2. Indeed, the pathogenic mechanisms associated with this virus require an integrative approach drawing on complementary disciplines such as transcriptomics, genetics, systems immunology, and bioinformatics.

To illustrate the complexity and breadth of emerging knowledge in this field, a diagram is proposed in Figure 3.15, connecting three of the disciplines mobilized in the study of SARS-CoV-2 and its short- and long-term effects. The text also illustrates the complexity of molecular biology. So that an inexperienced reader can grasp this complexity, Figure 3.15 also lists the acronyms used.

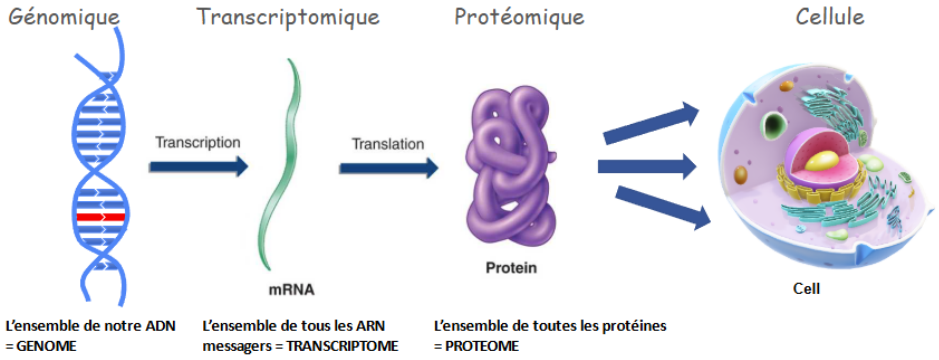


Figure 3.15 – Molecular biology—through genomics, transcriptomics, and proteomics—makes it possible to explore an organism's global response to an insult.

Recent advances in molecular biology have made it possible to better understand the immune mechanisms underlying complex viral infections, such as those induced by the HTLV-1 virus, viral–fungal pulmonary coinfections in patients with COVID-19 or influenza, as well as prolonged post-viral syndromes such as Long COVID. This review draws on four recent studies to illustrate the integration of transcriptomic, genetic, and immunological data in deciphering pathogenesis and in identifying biomarkers and therapeutic targets.

In a study by Assone *et al.* (2022), the authors analyzed inflammatory biomarkers in patients with HTLV-1–associated myelopathy (HAM/TSP) [104]. They identify *IL-17A* and *IFN-γ* as markers of active neuroinflammation, while *GlycA* and *TNF* appear as predictors of corticosteroid response. The use of machine learning algorithms made it possible to classify patients with an accuracy of 90.7 %, paving the way for a precision-medicine approach in this chronic condition.

In parallel, the study by Feys *et al.* (2022) explored mechanisms of innate immunity in viral–fungal pulmonary coinfections (IAPA and CAPA) [105]. An alteration of phagocytic functions—namely a decrease in neutrophils and repression of *IFN-γ* signaling—was observed in patients with invasive aspergillosis. Spatial transcriptomic analysis revealed

a breakdown of the epithelial barrier and a weakening of the local antifungal response, suggesting that exogenous *IFN-γ* could constitute a promising adjuvant therapy.

In a post-infectious context, Menezes *et al.* (2024) demonstrated the persistence of SARS-CoV-2 RNA in the blood of patients with Long COVID [88]. Transcriptomic analysis revealed persistent inflammatory signatures and identified candidate biomarkers allowing differentiation of post-acute states. These results suggest a residual inflammatory state that may contribute to prolonged symptomatology.

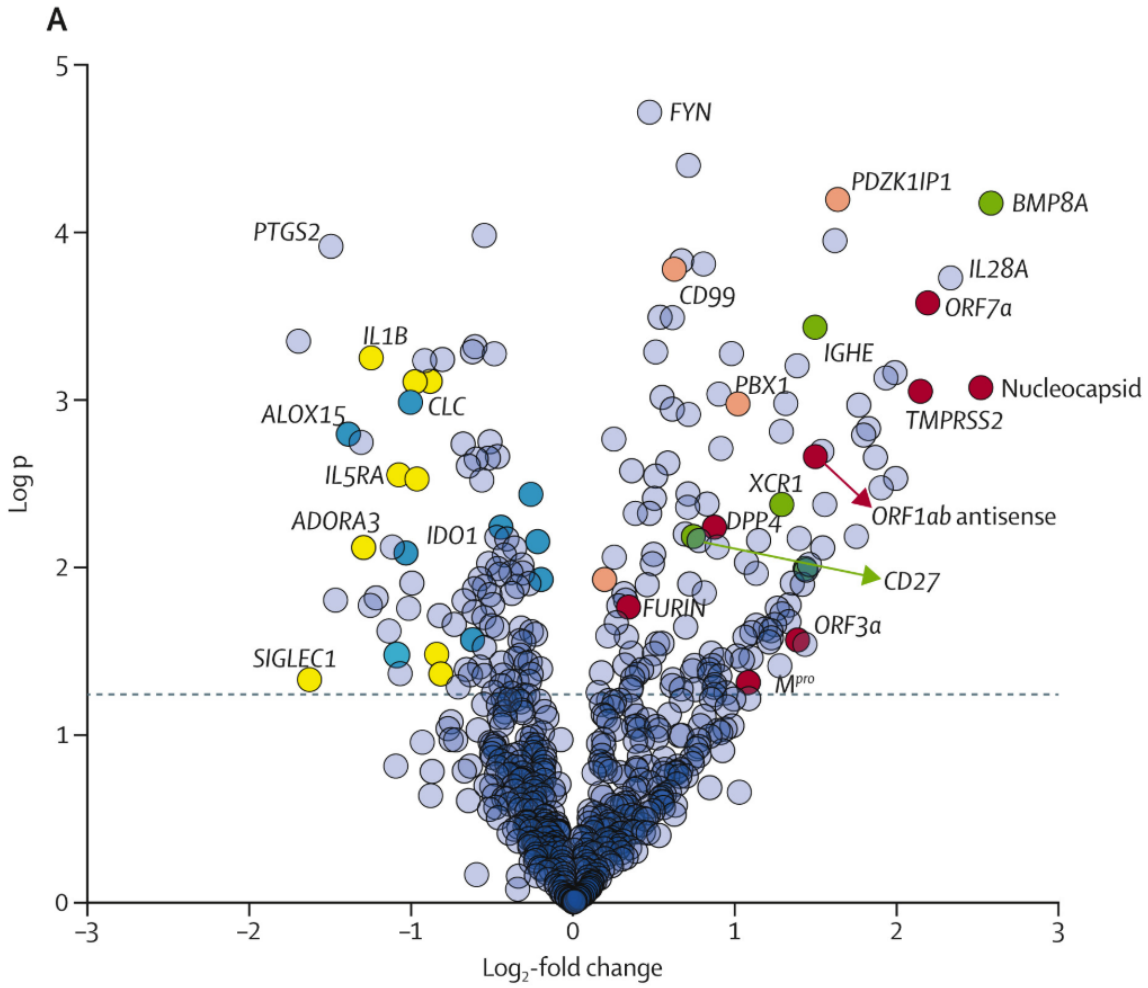


Figure 3.16 – Volcano plot of differentially expressed genes in whole-blood samples from individuals with long COVID (n=48) compared with control individuals (n=12) matched for age, sex, vaccination status, time since acute COVID-19, and number of comorbidities. Genes highlighted in red represent viral RNAs (nucleocapsid, ORF3a, ORF7a, Mpro, and antisense ORF1ab) as well as SARS-CoV-2–related host transcripts (ACE2/TMPRSS2 coreceptors, and the proteases DPP4 and FURIN). Notably, antisense ORF1ab transcripts are detected only when the virus is actively replicating [88].

Finally, the genetic study led by Schuermans *et al.* (2024) provides direct evidence of the link between genetic predisposition to thromboembolism and an increased risk of developing Long COVID [106] . Identification of the PAR-1 receptor as a potential mediator strengthens the hypothesis of coagulation and endothelial involvement in the pathogenesis of Long COVID.

These works converge toward a better understanding of the interactions between innate immunity, chronic inflammation, and genetics. The combined use of transcriptomics, population genetics, and machine learning enables precision medicine tailored to each patient's specificities

Acronym	Meaning
CAPA	COVID-19–Associated Pulmonary Aspergillosis
CIBERSORTx	Cell-type Identification By Estimating Relative Subsets Of RNA Transcripts
COVID-19	Coronavirus Disease 2019
FC GR1A	Fc Gamma Receptor Ia
GlycA	Glycoprotein Acetylation
HAM/TSP	HTLV-1–Associated Myelopathy / Tropical Spastic Paraparesis
HTLV-1	Human T-cell Leukemia Virus Type 1
IFN-γ	Interferon Gamma
IL	Interleukin (e.g., IL-2, IL-6, IL-10, IL-17A)
IAPA	Influenza-Associated Pulmonary Aspergillosis
nCounter	NanoString platform for measuring gene expression
NMR	Nuclear Magnetic Resonance
PAR-1	Protease-Activated Receptor 1
PBMC	Peripheral Blood Mononuclear Cells
PL HTLV-1	People Living with HTLV-1
RNA	Ribonucleic Acid
RNAScope	RNA in situ hybridization technology
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
STAT1	Signal Transducer and Activator of Transcription 1
TNF-α	Tumor Necrosis Factor Alpha

In plain language

Understanding the effects of SARS-CoV-2 through molecular biology

Classical biology has greatly helped us understand how the human body works. But with a virus as complex as SARS-CoV-2, that is no longer enough. Today we need to combine several fields: genetics, the study of which genes are active in cells (transcriptomics), how the immune system functions, and the computational analysis of large amounts of data.
Researchers use these techniques to better understand why some people develop severe forms of COVID, or symptoms that last long after infection (Long COVID).

- In people infected with other viruses such as HTLV-1, certain blood markers can indicate who will respond well to treatments.
- In patients with COVID-19 and fungal lung infections, the immune system is weakened, and one molecule (IFN-γ) could help them defend themselves better.
- In patients with Long COVID, elements of the virus are still present in the blood long after the illness, which could explain persistent symptoms.
- Genes related to blood coagulation may also play a role in the development of Long COVID.

This research helps us better understand what is happening in the body and tailor treatments to each patient. This is called *precision medicine*.

3.7 Proteomics and Multi-Omics Exploration of Long COVID: An Integrated Strategy Led by the Long COVID Belgium Network

Bart Van Puyvelde, PhD. Postdoctoral Researcher — Laboratory of Pharmaceutical Biotechnology, Department of Pharmacy (Faculty of Pharmaceutical Sciences, Ghent University)

Proteomics, using liquid chromatography coupled with mass spectrometry (LC-MS), enables large-scale measurement of the body's protein complement, offering a real-time readout of the biological processes involved in Long COVID [107]. Unlike genomics or transcriptomics, proteomics directly targets the functional molecules, particularly those involved in inflammation, immunity, and coagulation.

Among the biological pathways identified, the complement system appears abnormally activated in patients with Long COVID. Elevated soluble *C5bC6* complexes and reduced membrane complexes containing *C7* indicate increased activity of the membrane attack complex (MAC), potentially inducing cellular and tissue damage. These alterations are accompanied by thrombo-inflammatory markers, signs of endothelial dysfunction, and evidence of viral reactivation [108].

Proteomic and immune profiles measured during the acute infection phase have also proven predictive of the later onset of Long COVID, highlighting their diagnostic and prognostic value [109]. Nevertheless, current studies remain limited by small cohort sizes, lack of longitudinal follow-up, and a mono-omic approach that fails to capture the complexity of Long COVID, a systemic disease with many facets [110].

The Long COVID Belgium Network seeks to overcome these limitations by combining integrated multi-omics analysis (proteomics, transcriptomics, metabolomics, immunophenotyping) with comprehensive clinical data collection, including standardized questionnaires, cognitive assessments, and regular follow-up visits. This approach enables a systemic understanding of Long COVID.

Within this framework, we have implemented a dual proteomic strategy:

— **Targeted approach**: This aims to detect residual viral proteins in plasma using highly specific immunoaffinity reagents. Initially developed for SARS-CoV-2 detection in nasopharyngeal samples, this assay is being adapted to explore potential viral persistence in Long COVID patients [111]. Some analyses have already revealed the circulating presence of nucleocapsid protein, providing direct molecular evidence of viral antigen persistence. These results corroborate an earlier transcriptomic study by the consortium, which also identified circulating viral proteins (spike or nucleocapsid), strengthening the hypothesis of persistent viral reservoirs contributing to chronic immune activation [88].

— **Untargeted approach**: An exploratory analysis of plasma proteomics is used to profile host responses in an unbiased manner and to discover new pathophysiological pathways associated with persistent symptoms [112]. Initial datasets have already been collected and provide valuable insights. As the cohort expands and longitudinal data accumulate, our understanding of the molecular underpinnings of Long COVID is significantly enriched.

To interpret and contextualize these complex data, the contribution of the consortium's multidisciplinary group will be essential. Clinicians, immunologists, neurologists,

virologists, and *data scientists* will pool their expertise to translate molecular discoveries into concrete advances for patient care and treatment.

In plain language

Long COVID: How Protein Analysis Sheds Light on the Disease

To better understand Long COVID, Belgian researchers are using a technology called proteomics, which allows them to analyze the proteins present in the blood. These proteins are direct indicators of what is happening in our bodies: inflammation, immune defense, coagulation.

Through these highly precise analyses, scientists have discovered signs of abnormal immune system activation, and even, in some patients, the persistent presence of viral proteins such as the nucleocapsid protein, several months after infection. This could explain why symptoms persist in some people.

This innovative approach, led by the Long COVID Belgium consortium, is combined with comprehensive clinical follow-up. It could pave the way for better diagnosis of Long COVID and, ultimately, more targeted treatments.

3.8 Neurobiology: Involvement of IgG in the Neurological Symptoms of Long COVID

Charles Nicaise, Professor of Histology and Neurosciences, University of Namur
LNR Team, URPhyM, NARILIS, University of Namur

Principal Investigators:
Charles Nicaise (PI), Margaux Mignolet (FRIA PhD student)

Collaborations:
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Catherine Deroux (Neurology, CHU UCL Namur),
Nicolas Gillet (University of Namur),
Johan Van Weyenbergh (KU Leuven),
Marc Jamoulle (Family Physician, HEC-ULg & CAMG-UCL)

Summary: Preliminary results and research perspectives on the involvement of immunoglobulin G (IgG) in persistent neurological disorders observed in patients with Long COVID.

Involvement of IgG in the Neurological Symptoms of Long COVID

Based on the updated consensus definition from the World Health Organization (WHO), we recruit Long COVID patients presenting at least two neurological sequelae among the following: cognitive impairment, muscle or joint pain, fatigue, anxiety, or depression.

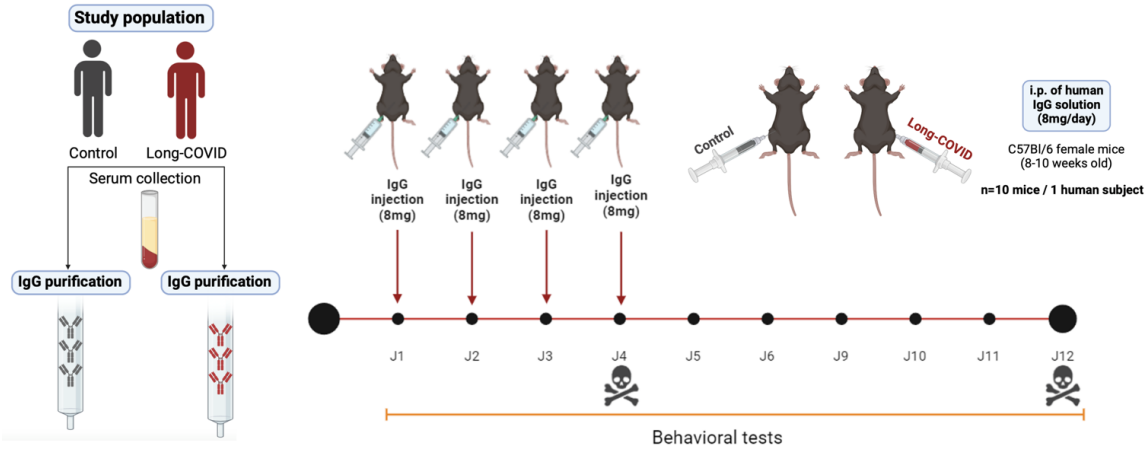

Figure 3.17 – Experimental design. IgG are purified and isolated from the serum of patients with neuro-Long COVID or from healthy age- and sex-matched individuals. These IgG (8 mg) are injected intraperitoneally into 8-week-old female C57Bl/6J mice. During the two weeks following the injections, behavioral tests are performed to assess cognitive functions and pain in the mice. $N = 10$ mice/patient.

As part of our research on the etiopathogenesis of Long COVID, our results suggest that the painful symptomatology experienced by patients is at least partially mediated by circulating autoantibodies. This has been demonstrated by the passive transfer of immunoglobulin G (IgG) from patients ($n = 10$) to laboratory mice. These results are based on the appearance of abnormal responses to mechanical stimuli (tactile allodynia) and thermal stimuli (thermal hyperalgesia) in the animals. These responses normalize after prior enzymatic destruction of the IgG or after injection of IgG-depleted serum.

In contrast, we have not observed any cognitive effects associated with the transfer of pathogenic IgG in this animal model. Although autoantibodies have been identified in severe acute COVID or in Long COVID cohorts [113, 114], their persistence, their functionality over time, and their pathogenic potential toward cells or structures of the central or peripheral nervous system remain to be determined. Our demonstration of a pain-mediated effect by IgG is supported by convergent results from independent teams in the United States and the Netherlands [115, 116].

We are currently working to identify, both in our Long COVID animal model and in human post-mortem samples, the binding sites of pathogenic IgG, as well as the potentially recognized epitopes. In parallel, we are investigating traces of sequelae in the nervous system of the animals, searching for markers of neuroinflammation or glial activation.

In this experimental protocol, human immunoglobulin G (IgG) are purified from the serum of patients with neuro-Long COVID as well as from healthy age- and sex-matched controls. These IgG are then injected intraperitoneally into 8-week-old female C57Bl/6J mice, at a dose of 8 mg per day for four consecutive days. Following these injections, the animals are monitored for two weeks, during which behavioral tests are conducted to assess cognitive functions and pain-related responses. Each batch of mice ($N = 10$) corresponds to the IgG from a single human donor. This model aims to explore the potential involvement of human IgG in the pathophysiology of Long COVID.

A second line of research focuses on identifying biomarkers of neurological sequelae in the serum of Long COVID patients, following the work of Peluso et al. [117]. Our preliminary results, obtained from more than 130 Belgian patients, show elevated levels of GFAP (glial fibrillary acidic protein), while Nf-L (neurofilament light chain) and UCH-L1 (ubiquitin carboxy-terminal hydrolase L1) levels remain comparable to those of the control population (unpublished data). We aim to correlate these serum biomarkers with patients' clinical presentations and to evaluate their prognostic potential.

e

In plain language

What do our neurobiological studies reveal about Long COVID?

- We study Long COVID patients who present neurological symptoms such as fatigue, pain, or memory disturbances.
- Our results suggest that some antibodies produced by the body may be involved. When these antibodies are injected into mice, they develop abnormal pain sensitivity but no cognitive impairment.
- We aim to identify where these antibodies act in the nervous system and whether they cause brain inflammation.
- In addition, in the blood of more than 130 patients, we detected a marker of brain inflammation (GFAP), which could help better understand the disease and predict its course.

3.9 Immunological Profiling: Untangling Severe Forms of Long COVID

By Petter Brodin, Head of the Systemic Immunology Research Group, Imperial College, UK & Karolinska Institutet, Sweden. Translated from English by Marc Jamoulle

Introduction

The COVID-19 pandemic has left many individuals struggling with persistent symptoms long after recovering from the initial infection, a condition now referred to as *Long COVID*. While clinical manifestations vary widely, some individuals develop severe and disabling forms. This study investigates the hypothesis that viral persistence could be a major causal factor [118].

Methodology

The study was conducted as part of the international *COVID-Human Genetic Effort* (CHGE[1]), with a cohort of 121 patients (Belgium, $n = 31$; Sweden, $n = 90$), primarily women (87%), with a mean age of 48 years (14 to 72 years). The cases included measurable abnormalities such as:

— Microvascular dysfunction (cardiac MRI),

— Endothelial dysfunction (EndoPAT),

— POTS, hyperventilation, pulmonary abnormalities (CT scan, DLCO).

Comparisons were made with individuals fully recovered from mild COVID-19 infections [119, 120].

Key Results

1. High antibody activity Severely affected patients had significantly higher levels of anti–SARS-CoV-2 IgG antibodies compared to controls. This persistence suggests a prolonged immune response, supporting ongoing activation by viral antigens [121].

2. Detection of viral fragments Viral proteins (Spike, N) and viral RNA were detected in the blood of 10–20% of patients. However, detection was not consistent, indicating:

— either insufficient test sensitivity,

— or viral presence confined to tissues,

— or true heterogeneity in viral persistence.

These observations are supported by post-mortem studies [122].

3. Altered $CD8^+$ response Patients with high IgG levels showed a reduced virus-specific $CD8^+$ T cell response. These T cells appeared "restrained": they expressed fewer cytotoxic molecules and more regulatory/suppressive immune markers. This could explain the inability to clear viral antigens, maintaining chronic immune stimulation [123].

1. `https://www.COVIDhge.com/`

Conclusion

This study supports the hypothesis of viral persistence underlying severe forms of Long COVID. Failure to fully eliminate the virus may sustain chronic and symptomatic immune activation. Clinical trials of antivirals appear justified [124].

In plain language

IN-DEPTH IMMUNOLOGY OF LONG COVID

A study conducted in Belgium and Sweden on 121 Long COVID patients shows that their immune system remains activated several months after the initial infection. Findings include:

— persistently high antibody levels,

— occasional traces of the virus,

— and immune cells that fail to clear it.

This suggests that the virus might remain hidden in certain tissues and that antiviral treatments could help these patients.

3.10 Genomics and Long COVID

By Aurélie Cobat, MD, PhD. Research Scientist (CRCN) at INSERM, within the Laboratory of Human Genetics of Infectious Diseases (Inserm U1163), Imagine Institute, Paris.

There is considerable interindividual variability in response after SARS-CoV-2 infection, ranging from asymptomatic forms to severe disease threatening vital prognosis. Sociodemographic and clinical factors alone cannot explain this immense clinical heterogeneity. With the international consortium *COVID Human Genetic Effort* (CHGE, `https://www.COVIDhge.com`), we are testing the hypothesis that some severe forms of COVID-19 (such as hypoxemic pneumonia, multisystem inflammatory syndrome in children (MIS-C), or even Long COVID) could be caused, in certain patients, by monogenic inborn errors of immunity to SARS-CoV-2 [125, 126].

Our general strategy relies on exome or genome sequencing of patients with severe forms. The identification of candidate variants relies on an optimized filtering strategy combining multiple criteria at the variant level (frequency in public databases, functional annotation, pathogenicity prediction scores) and the gene level (e.g., level of negative selection). We search for genes enriched in candidate variants among patients compared to control individuals, using statistical methods aggregating variants within genes. The most promising genes and variants are then subjected to functional studies to validate their potential role in disease susceptibility [127].

Our work on COVID-19 pneumonia has provided proof-of-concept that rare genetic defects can render certain individuals more vulnerable to severe forms. We established the central role of type I interferons (IFNs) in the acute immune response against SARS-CoV-2 and identified a new inborn error of immunity affecting this pathway: the X-linked *TLR7* deficiency [128].

In total, deleterious genotypes in 13 loci linked to the type I IFN pathway are responsible for severe COVID-19 pneumonia: *TLR3, TLR7, UNC93B1, TBK1, TRIF, IRF3, IRF7, IFNAR1, IFNAR2, STAT2, TYK2, IRAK4, MYD88* [126, 127]. These inborn errors of immunity account for about 1 to 5 % of life-threatening pneumonia cases, particularly in patients under 60 years old, with the X-linked *TLR7* deficiency alone explaining more than 1 % of severe cases in men [128].

These discoveries led us to explore other mechanisms potentially impairing the type I IFN pathway, especially in elderly patients. We thus highlighted the presence of autoantibodies neutralizing type I IFNs in about 15 % of unvaccinated patients with severe COVID-19 [129, 130]. In the general population, their prevalence is low before age 65 (1–2 %), but exceeds 6 % after age 80 [130]. These autoantibodies are major risk factors for severe COVID-19 at all ages, with relative risks exceeding 20 [130].

To date, the genetic basis of Long COVID remains poorly understood. Building on our previous work, we have launched a sequencing study in patients with Long COVID. To maximize the chances of identifying genetic determinants, we focus on patients with severe involvement documented by imaging, physiological, or biochemical tests, not explained by the severity of the acute phase or by treatments received [131].

Identifying genetic defects predisposing to severe forms of Long COVID could help better understand the disease's pathophysiology and shed light on other post-infectious syndromes.

In plain language

Role of genetic factors in the response to COVID-19

+ Reactions to COVID-19 vary widely between individuals. While age or chronic conditions explain part of this variability, genetic factors also play a major role in susceptibility to severe disease.
+ Research has shown that some individuals carry rare genetic abnormalities that weaken their immune system, particularly type I interferon production, a key antiviral defense. For example, mutations in the *TLR7* gene, located on the X chromosome, make certain men more vulnerable to severe disease.
+ In addition, autoantibodies neutralizing interferons have been identified in about 15 % of unvaccinated patients with severe COVID-19. These autoantibodies are more frequent in the elderly, exceeding 6 % after age 80.
+ Regarding Long COVID, genetic causes remain poorly understood. Ongoing studies are analyzing the genome of patients with persistent symptoms to identify possible genetic predispositions [131]. This research could also shed light on other post-infectious syndromes.

3.11 Brain Scintigraphy versus PET Scan in Long COVID Patients

Exploring Vascular Endothelitis in Long COVID

Recent publications have shown that SARS-CoV-2 infection induces alterations in vascular endothelial function [132, 133, 134]. Inflammation of the endothelium, platelet hyperactivation, and microclot formation are characteristic of this persistent vascular involvement. Chronic endothelitis could contribute to hypercoagulability and vascular complications in Long COVID.

The Role of Brain Imaging

To document these alterations, two nuclear imaging techniques are currently available:

— PET scan with fluorodeoxyglucose (18F-FDG), which assesses brain metabolism.

— Brain scintigraphy with technetium (SPECT-CT), which evaluates cerebral perfusion.

PET scans have shown regional hypometabolism in patients with post-COVID neurological involvement [135, 136]. Although considered the gold standard, PET scans are not easily accessible: they are expensive, prescribed only by neurologists, and not reimbursed in Belgium for Long COVID indications.

In primary care, only brain scintigraphy with technetium remains available. This older technique relies on the injection of technetium-99m (Tc-99m) tracers, which bind to brain tissue according to blood flow. Although its resolution is lower than PET scans, it can reveal anomalies consistent with chronic cerebral hypoperfusion.

Clinical Interpretation and Limitations

In practice, brain scintigraphy has been requested in patients with severe functional impairment. MRI and CT scans are often normal in these contexts, highlighting the value of nuclear methods. It should be noted that one patient initially diagnosed with Alzheimer's disease had two abnormal brain scintigraphies while both PET scans were normal (personal communication, Dr. Guedj).

The choice of imaging modality should consider the presumed vascular nature of Long COVID: PET evaluates neuronal metabolic activity, whereas technetium brain scintigraphy documents perfusion disorders — consistent with chronic endothelitis.

Criterion	SPECT-CT (Technetium)	18F-FDG PET Scan
Tracer Used	Technetium-99m HMPAO [2]	Fluorodeoxyglucose (18F) [3]
Action	Absorbed by brain tissue in proportion to blood flow	Absorbed by brain tissue in proportion to glucose metabolism [4]
Target	Assess blood flow	Assess metabolism
Radiation Type	Emits gamma rays	Emits positrons
Irradiation Time	6-hour half-life	Longer body retention, about 2-hour half-life
Linear Energy Transfer (LET)	Lower	Higher [5]
Economic Cost	145 to 450 €	800 to 1,200 €
Environmental Cost	++	++++ [6]

Table 3.7 – Comparison between SPECT-CT (Technetium) and 18F-FDG PET Scan

In plain language

Long COVID: What Do Brain and Vascular Imaging Exams Tell Us?

- **Long COVID** may be linked to inflammation of blood vessels (*endothelitis*), leading to circulatory disorders, microclot formation, and lasting neurological symptoms.
- **Brain imaging tests** can explore these disorders.
- **PET Scan** (*TEP*):
  - measures brain activity via glucose consumption;
  - is highly accurate but costly and less accessible;
  - requires heavy equipment (cyclotron), generating radioactive waste.
- **Technetium brain scintigraphy** (*SPECT-CT*):
  - visualizes **cerebral blood flow**;
  - is more accessible, especially in primary care;
  - is less expensive and less polluting than PET scans;
  - can detect anomalies when MRI, CT, or PET scans are normal.
- Although sometimes considered outdated, scintigraphy has shown **clinical usefulness in Long COVID patients** with cognitive disorders or persistent fatigue.
- In a context where Long COVID is seen as a **cerebrovascular disorder**, scintigraphy represents a **relevant and pragmatic imaging tool** in primary care.

3.12 Neuro-Metabolic Alterations Observed in Magnetic Resonance Spectroscopy (MRS) in Patients with Long COVID

by Jean Marc Constans MD, PhD. Department of Neuro-Radiology and Medical Imaging, University Hospital of Amiens, France

It is important to assess the complications of COVID-19 on the nervous system in order to identify and understand the neurobiochemical mechanisms that may be responsible for persistent neurological symptoms. Magnetic Resonance Spectroscopy (MRS) is an extension of Magnetic Resonance Imaging (MRI) used to analyze metabolites present in tissues in a non-invasive way.

In the context of Long COVID, MRS is particularly useful for studying brain metabolic abnormalities in patients with persistent neurological symptoms [137]. MRS helps to identify metabolic alterations associated with Long COVID, to understand the biochemical mechanisms responsible for persistent neurological complications, and to assess the sensitivity of MRS compared to MRI in diagnosing these abnormalities.

As part of the "N-SPECTRO-COVID" project at Amiens-Picardie University Hospital, MRS is used to target specific metabolites such as choline, creatine, lactate, and N-acetyl-aspartate (NAA). A comparative analysis of metabolic spectra in Long COVID patients versus control individuals is performed.

In Long COVID research, the University Hospital of Amiens already has substantial expertise regarding MRI variations that highlight neurocognitive disorders in these patients [138]. An MRS study has already been conducted, revealing tissue and metabolic abnormalities linked to persistent neurological symptoms in Long COVID patients. About a dozen clinically identified Long COVID patients from our Belgian cohort have access to MRS at Amiens as part of this research.

Interpretation of Brain Magnetic Resonance Spectroscopy (MRS)

Magnetic Resonance Spectroscopy provides a biochemical profile that usefully complements conventional morphological imaging (MRI).

— **N-acetyl-aspartate (NAA)**: Marker of neuronal viability. A decrease suggests neuronal distress or loss of neuronal density.

— **Choline (Cho)**: Reflects membrane turnover. Its elevation is common in inflammation, gliosis, or cellular proliferation.

— **Creatine (Cr)**: A stable metabolic reference used to calculate ratios (e.g., Cho/Cr, NAA/Cr).

— **Lactate (Lac)**: Indicator of anaerobic metabolism. Significant presence indicates metabolic stress, tissue hypoxia, or inflammation.

— **Glutamate-Glutamine (Glx, including Gln)**: Reflects excitotoxicity, inflammation, or neurotransmitter imbalance, often seen in encephalopathies.

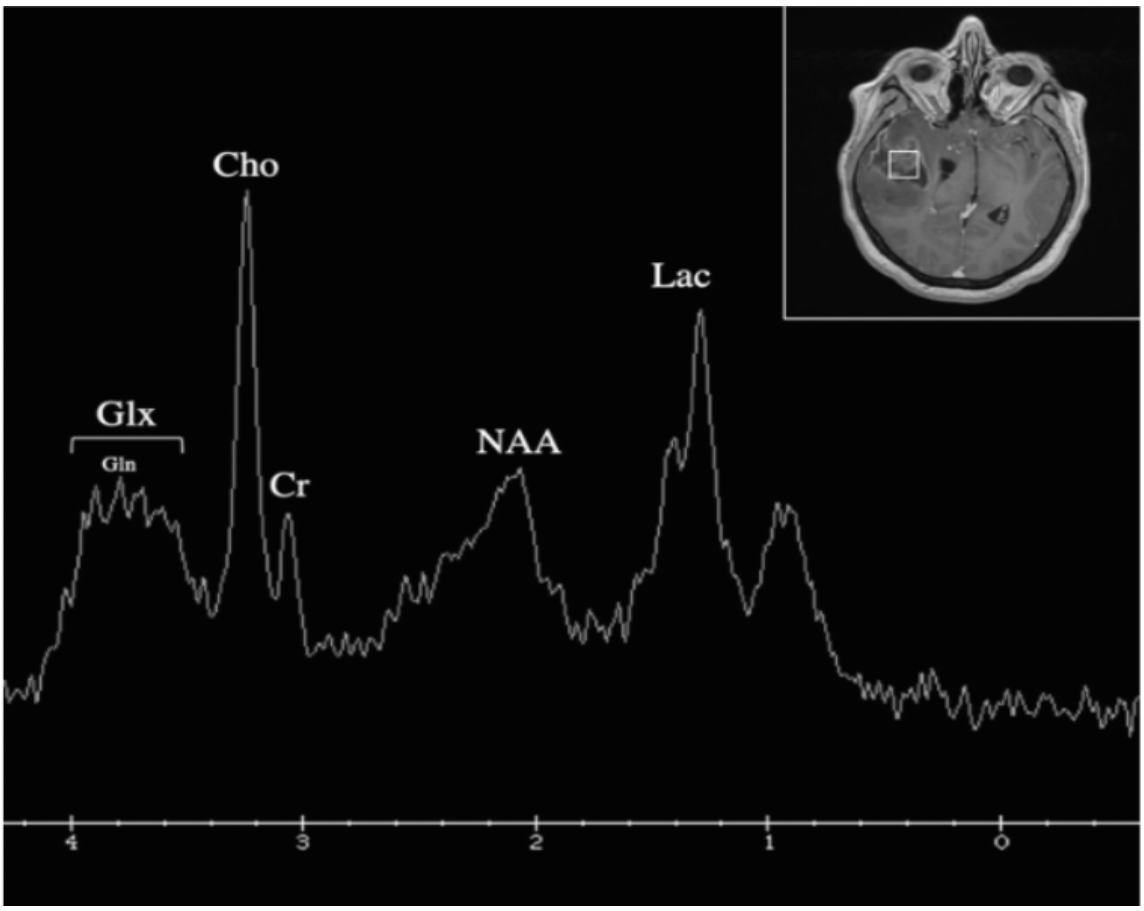

Figure 3.18 – Brain MRS illustrating the main metabolic peaks observed (Cho, Cr, NAA, Lac, Glx). The inset in the upper right corner shows the anatomical location of the studied voxel.

Analysis of the observed spectrum. The spectrum shown in Figure 3.18 presents several characteristic peaks obtained from a localized brain region (visible on the anatomical MRI inset). The identified metabolites are as follows:

— **Choline (Cho)**: The peak is clearly elevated, suggesting increased membrane turnover, often seen in inflammatory processes or gliosis.

— **Creatine (Cr)**: The peak is present and serves as a reference for metabolic ratios.

— **N-acetyl-aspartate (NAA)**: The signal is moderate, lower than choline, which may indicate functional neuronal distress or reduced neuronal density.

— **Lactate (Lac)**: The peak is clearly visible as a doublet at 1.3 ppm, indicating increased anaerobic metabolism. This may reflect cellular stress, hypoxia, or a local immune response.

— **Glx (glutamate-glutamine)**: The signal is identifiable, notably before the choline peak. It indicates a glutamatergic imbalance, sometimes associated with neuroinflammatory conditions.

The overall profile is compatible with a *non-lesional post-infectious encephalopathy*. In the context of Long COVID, it supports the hypothesis of a chronic neuroimmune or metabolic process, possibly related to viral persistence or dysregulation of the central inflammatory response.

In plain language

Long COVID and Brain Imaging: The Role of Magnetic Resonance Spectroscopy (MRS)

+ COVID-19 can leave lasting effects on the brain, such as memory, concentration, or mood disorders.
+ To better understand these effects, researchers use an advanced technique: **Magnetic Resonance Spectroscopy (MRS)**.
+ MRS is an enhanced version of MRI that not only shows brain images but also reveals its internal chemistry.
+ It analyzes substances in the brain (called *metabolites*) and detects abnormalities linked to *Long COVID*.
+ At the Amiens University Hospital, a study involving Belgian Long COVID patients aims to identify chemical imbalances in certain brain regions.
+ These abnormalities are associated with persistent neurological symptoms observed clinically.
+ Comparisons are made with healthy subjects to identify neurochemical differences.
+ MRS specifically targets compounds like *choline*, *creatine*, *lactate*, and *N-acetyl-aspartate*, whose levels may change with inflammation or cellular damage.
+ These analyses help refine diagnosis and open new therapeutic perspectives.

3.13 Anthropology: Societal Impact of Long COVID, Patients' and Medical Community's Perceptions

By Olivier Schmitz (CAMG-UCL), Gisèle Kazeneza Mugisha (ULB), and Marc Jamoulle (CAMG-UCL & HEC-ULg)

3.13.1 Life with Long COVID: A Sociological Perspective

> *I also sometimes say words different from what I mean to say. The other day I wanted to say, "I can't write because I don't have my glasses"... and I said: "I can't write because I don't have ears."*
>
> — M. Jamoulle, consultations, 2025

An "emerging" nosological entity, Long COVID has now joined the class of complex chronic conditions with devastating effects on patients' individual and social lives. It manifests both as a biological disorder affecting multiple systems (immune, muscular, neurological, cognitive, psychological) and as a sociological revealer of dysfunction in our health systems [139].

After acute COVID, patients experience a profound and distressing transformation of daily life. Sometimes very active or athletic before the illness, they feel persistent symptoms that neither they nor their physicians understand. Many do not feel believed or cared for [140]. Redirected to psychiatry due to their psychological suffering, they often receive diagnoses such as depression, burnout, or mixed anxiety–depressive disorder, with treatments that are ill-suited [141].

Perplexed, family physicians struggle to recognize a new, stable yet atypical symptom pattern. Long COVID affects women more, targets blood vessels, the immune system, and the hippocampus—impairing working memory, the cradle of individual identity. Patients find themselves "out of the race," excluded from their social role [142].

Long COVID cannot be reduced to a simple biological pathology: it exacerbates social vulnerabilities, warranting a biosocial analysis [143]. By heightening inequalities in access to care, it reveals mechanisms of abandonment. The English term "gaslighting" describes medical denial of the patient's symptoms, which here can be rendered as "medical symbolic violence" [144, 145].

Health systems are not yet structured to deal with uncertain and evolving diagnoses. Insurance and occupational recognition policies for Long COVID remain timid, generating lived injustices [146].

3.13.2 A Qualitative Study on Belgian Patients' Lived Experience

In July 2021, Ms. Gisèle Kazeneza Mugisha (family medicine trainee, UMONS) conducted a qualitative study on six Long COVID patients seen in consultations in Charleroi. The interviews, guided by a dedicated questionnaire, were transcribed and analyzed under the supervision of Prof. Olivier Schmitz. One patient underwent longitudinal follow-up over three years. A return to the six patients is planned at four years [147]. Selected interview excerpts help grasp the complexity of patients' lived experience; here are a few.

"I'm so tired, I'm no longer myself, I can't run, not even walk fast..."
"My view of my body and of the medical world has changed..."
"I have a headache like a leaden weight..."

"My leg moves on its own... my feet tingle..."
"I hate doctors, they never listen to me..."
"After 31 years of work, I'm on disability and earn barely 50% of my salary..."

These accounts illustrate the experience of a condition that is both medically uncertain and socially disqualifying.

In plain language

Living with Long COVID

Long COVID is a recent, still poorly understood illness that can last for months or even years. It causes extreme fatigue, pain, memory problems, shortness of breath, anxiety... It affects women in particular and upends lives.
But beyond the body, Long COVID also disrupts social life and the relationship with medicine. Many say they are not believed or listened to, or are told it's "all in their head." This leads to misdiagnoses and inappropriate treatments.
A Belgian sociological study is following several patients over multiple years. The aim: to understand what Long COVID reveals about weaknesses in our health system, and how to better support these patients.
Testimonies collected:

— "I'm no longer myself..."

— "I can't walk fast anymore..."

— "I have a headache like a leaden weight..."

— "I can't retain anything at school anymore..."

— "I hate doctors, they never listen to me..."

These accounts show that Long COVID is not only a medical problem, but also a social and human one. It calls for an open, attentive approach and a transformation of the care system.

3.14 Epidemiology, Biostatistics, and Long COVID

By Pamela Mfouth Kemajou (UGent), Olivier Latignies (IRSS ULB), and Marc Jamoulle (CAMG-UCL & HEC-ULg)

Epidemiology

Worldwide, estimates of the prevalence of **COVID** ; Coronavirus Disease
Long COVID vary due to differences in methodologies, populations studied, and definitions used. A meta-analysis published in January 2025, based on 144 studies, estimated a weighted global prevalence of 36 % among people who tested positive for COVID-19 (95 % confidence interval [CI]: 33–40 %) [148]. This analysis highlighted geographic variations and shows that the prevalence of Long COVID does not decrease significantly over time. Identified risk factors include lack of vaccination, pre-existing comorbidities, and female sex.

In the European context, the prevalence of Long COVID is particularly significant. The **OMS** ; Organisation Mondiale de la Santé
estimated that at least 17 million people in the 53 Member States of the WHO European Region were affected by Long COVID between 2020 and 2021 [149]. A report by the **OCDE** ; Organisation de Coopération et de Développement Économiques
indicates that from 1/6 to 1/3 of patients have persistent symptoms more than 12 weeks after infection. Each year, more than 7 million quality-adjusted life years (**QALY** ; Quality-Adjusted Life Year
) are lost in OECD member countries [150].

In Belgium, data remain limited. A study by the Clinical Research Unit of Brugmann University Hospital (Brussels) identified patient clusters to tailor management [151]. A study using data from the Sentinel General Practitioners (SGP) network indicates that by the end of 2023, more than 1,000 patients had entered a post-COVID care pathway. Fewer than 10 % benefited from multidisciplinary follow-up [152].

Illustrative comparative prevalence data

Region / Study	Estimated Prevalence	Source
World (144 studies)	36 % (95 % CI: 33–40)	Hou et al. (2025)
WHO Europe	17 million people	WHO, 2022
OECD	1/6 to 1/3 of cases >12 wks	OECD, 2022
Belgium (SGP)	1,000 patients end of 2023	Moreels et al. (2024)

Table 3.8 – International comparison of Long COVID prevalence estimates

Clinical Data Management in Service of the Network

The question of populations at risk of developing Long COVID has been the subject of several studies. In Belgium, Nayani et al. identified certain factors associated with this condition, notably female sex, a history of chronic diseases or mental health disorders, as well as hospitalization for SARS-CoV-2 infection [153]. However, a larger meta-analysis retains only three significant factors increasing the risk of Long COVID: disease severity (including hospitalization), length of hospital stay, and female sex, with the majority of those affected being women [154]. A more recent meta-analysis also identifies three

risk factors: female sex, pre-existing comorbidities, and lack of vaccination. This study highlights heterogeneity of estimates across populations and regions, underscoring the need for rigorous follow-up based on representative global studies [155].

However, heterogeneous structuring of health data and the use of terminologies specific to countries and health institutions are major obstacles to multicenter studies and effective sharing of data, methods, and results. A recent survey conducted in 9 high-income countries (Belgium, Canada, Germany, Italy, the Netherlands, New Zealand, Sweden, Switzerland, and the United Kingdom) qualitatively analyzed 17 longitudinal Long COVID datasets and decried the lack of data harmonization and insufficient political interest in creating patient registries [156].

Moreover, the study notes that no country has yet developed a comprehensive long-term data collection system to address research questions on Long COVID management. In most countries, data collection is ending, leaving a gap. In the face of these difficulties, initiatives such as those led by the Observational Health Data Sciences and Informatics (OHDSI) consortium aim to standardize data structures and vocabularies, promote reproducible and collaborative research, and share methods, tools, and results [157].

In this dynamic, HL7 (Health Level Seven) International and the OHDSI collaborative have implemented a common data model, the Observational Medical Outcomes Partnership (OMOP), enabling harmonized collection and sharing of clinical information. This initiative seeks to integrate clinical data into large repositories for advanced analysis, while limiting information loss due to successive conversions between different data models [158]. Harmonizing and standardizing data from diverse health systems internationally is therefore an essential lever for better understanding factors associated with Long COVID and identifying potential treatments that foster clinical remission.

The COVID-19 pandemic highlighted the crucial importance of electronic health data in managing health crises, accelerating the development of numerous digital solutions in this field. In response to this growing need, on May 3, 2022, the European Commission presented a legislative proposal to create a unified digital health market within the European Union. The European Health Data Space (EHDS) aims to strengthen EU citizens' control over their electronic health data and facilitate access to them to spur the development of innovative health services and products. This initiative takes into account both the primary use of data (health care) and secondary use (research and innovation), thus requiring the establishment of interoperability standards for national digital health infrastructures. These requirements will also apply to third-party providers from industry and academia to ensure seamless system integration [159].

On January 21, 2025, the European Council adopted a regulation strengthening citizens' privacy protection within the European Health Data Space (EHDS), thereby ensuring greater trust in this initiative. For example, a right of withdrawal was established for the primary use of data, allowing patients to limit access to their health information by professionals, except in cases of vital necessity. In addition, data reuse may be restricted by citizens, except for specific purposes such as research in the public interest [149].

In this perspective, our project is part of a process to standardize primary care health data from patients with Long COVID according to the OMOP model (see Figure 2.6). In the long term, this initiative aims to facilitate the integration of these health data into the EHDS, paving the way for a better understanding of risk factors and improved management strategies.

In plain language

Our project: structuring Long COVID data

Studies show that some people are at higher risk of developing **Long COVID**, meaning symptoms that last for several months after infection.
Risk factors include:

- being a woman,
- having chronic health problems (such as asthma or diabetes),
- not being vaccinated,
- or having been hospitalized for COVID,
- meeting a physician who knows Long COVID [160]

These results vary from one country to another.
To better understand this disease, we need to **bring together and compare health data at scale**.
Researchers have created tools to organize data uniformly, such as the **OMOP (Observational Medical Outcomes Partnership) model**.
In Europe, the **European Health Data Space (EHDS)** will allow everyone to better control their data while supporting research.
Our project aims to structure data from Long COVID patients so they can be shared and used across Europe.

3.15 Long COVID as a Revealer: Epistemological Issues of an Emerging Pathology

By Marc Jamoulle, family physician, Martin Spanoghe, geneticist, expert patient, Bram Rolus, engineer, expert patient, Paul Thielemans, internist, Daniel Widmer, family physician.

A persistent disease with systemic consequences

Long COVID refers to a persistent set of multisystem symptoms occurring after an acute SARS-CoV-2 infection, regardless of the initial severity. Affecting about 10 to 20% of infected individuals, it constitutes a major public health challenge [161]. It affects millions of patients worldwide, compromises their quality of life, reduces their ability to work, and generates considerable economic, social, and political costs. Its institutional recognition, however, remains uneven, and both medical and policy responses struggle to take shape [162, 163].

> *Sometimes I have difficulties... I have trouble thinking of something, reflecting on someone... I can no longer find solutions the way I used to: I was much faster at that. And what I also struggle with is forgetting certain things. I forget and think: well, how can that be? What did I come here to do? I don't know anymore... That happens to me. Sometimes my son tells me something, and afterward I no longer know what he said. Oh yes, he said that, but then... In the past, I had a good memory.*
>
> — M. Jamoulle, consultations, 2025

A fracture between science and medical practice

In this context, the medical community's attitude toward Long COVID raises profound questions and calls for a genuine epistemological reflection. While many scientists from the fields of HIV and immunology have turned to the study of SARS-CoV-2 and its prolonged consequences, part of the medical profession remains in a persistent ignorance that at times borders on scientific denial [145]. Many patients express a sense of abandonment, saying they are shuttled from specialist to specialist without clear recognition of their condition [164].

A gulf is widening between patients and caregivers, but also between clinicians and researchers. Never has a pathology prompted so many publications in such a short time and yet a majority of health professionals—generalists and specialists alike—remain in a state of ignorance that sometimes verges, if not on obscurantism, then on a hardly comprehensible indifference. Some adopt stances of distrust [165] toward scientific data, a mistrust that paradoxically fosters defensive medicine rather than medicine grounded in trust and dialogue. This defensive medicine [166], born of risk aversion and a climate of mutual suspicion, further weakens the therapeutic bond and drives clinical practice away from research, to the detriment of the patient.

> Testimony from a 38-year-old patient, language teacher;
> *When I have a "crash," the symptoms are almost always the same: overwhelming fatigue, a burning sensation in the brain, the feeling of molten lead flowing through my veins, pain in my hands and feet, memory and speech problems, difficulty walking,*

occasional hair loss, chest pain near the heart, and since September, breathing problems. But there are times when I feel perfectly fine, and I make the most of it. Overall, it's getting better—slowly but surely. I was first infected in October 2020.

— M. Jamoulle, Consultation, 2024

Toward a quiet biological revolution

Several factors can help explain this situation. From a scientific perspective, we are witnessing a genuine qualitative leap. Biologically, the rise of genomics, transcriptomics, proteomics, systems immunology, and neurobiology is upending traditional frameworks for understanding disease [167]. In this context, managing Long COVID requires rethinking diagnostic paradigms. It leads to the rehabilitation of imaging tools sometimes considered outdated, such as SPECT-CT brain scintigraphy [4]—which remains, in some cases, the only modality to reveal perfusion abnormalities—while also drawing on cutting-edge technologies such as functional MRI (fMRI) [83], magnetic resonance spectroscopy (MRS) [86], or fluorodeoxyglucose positron emission tomography (18F-FDG PET) [168], capable of detecting metabolic, neuroinflammatory, or energetic alterations invisible to conventional exams. However, the speed with which these advances unfold in basic research contrasts with their still limited diffusion in routine clinical practice.

Fragmented care in a hyper-specialized system

Several times I have the impression that my house is on fire. It's like a fog in front of my eyes, it comes on suddenly and after that... I can't do it anymore. After one page of a novel, or even if I manage two pages, I've already forgotten: who is Mr. and Mrs.? Who is doing what? I no longer know what I like. I can't read a novel anymore. I lose track after fifteen or twenty minutes. Picking up a series again isn't worth it.

— M. Jamoulle, consultations, 2025

From an organizational standpoint, the dominant biomedical model has historically developed along a logic of progressive specialization. While this specialization has enabled major advances in understanding pathophysiological mechanisms and in targeted treatments, it has also contributed to fragmented care. The patient is no longer understood as a whole person but as an aggregation of biological systems, each falling within a distinct field of expertise [169]. This compartmentalized organ-based approach—typical of hospital medicine—proves ill-suited to complex, multisystemic, evolving pathologies such as Long COVID.

This fragmentation is reinforced by an increasing technologization of care, in which the clinical relationship is often relegated behind paraclinical testing, and by a commodification of the health system [170], where economic logics, profitability, and productivity often guide care pathways. One might fear that, behind a proclaimed care ethic, the patient is treated primarily as an exploitable resource. The result is medical wandering, with patients cycling between generalists and specialists, without anyone taking charge of the entire clinical picture or accepting responsibility for overall coordination [171].

Moreover, medical information—which should be a common good serving both health professionals and citizens—is still largely structured and disseminated by the pharmaceutical and device industries. This highlights structural biases shaping the production and diffusion of health knowledge [172]. Conflicts of interest, ghostwriting, or selective promotion of favorable data contribute to a skewed view of clinical reality and at times

institutionalized unawareness. In the case of Long COVID, the lack of immediate therapeutic profitability may have dampened industrial interest and thus the condition's visibility in medical circles.

Against fragmentation, a comprehensive and protective medicine

> *I sleep much more than before. Before, I only slept at night; now I sleep almost all the time. Even after an activity or a game, I often have to go sleep. But I sometimes feel heavy... It's as if my whole body is flattening me, I don't know how to explain it, all flat... Sometimes when I climb the stairs, I'm very short of breath, like an old locomotive. ... I've already had fainting spells: I fall to the ground, I don't realize it, I see everything go black, like a beehive. When I wake up, I realize I've fallen... ... Before, I was good at school. Now, I tire quickly. Mom makes me review lessons: sometimes I say anything, like "1+1=3." Then, the next day, it comes back correctly.*
>
> — M. Jamoulle, Consultation 2025 (11-year-old child)

In the face of these dead ends, many professionals call for a reorientation toward a more holistic, comprehensive, relational medicine—centered on the person rather than the organ. This shift entails revaluing the first level of care, in which general practice and the family physician play an essential role. Through proximity, territorial anchoring, and an intimate knowledge of patients' histories, the general practitioner can ensure cross-cutting coordination, manage fragmented medical information, guarantee continuity of care, and contextualize complaints within the person's life trajectory [173].

As stated in the WONCA Europe Declaration;

> *General practice [...] is person-centered, community-oriented, and manages health problems at an early and undifferentiated stage. It ensures continuous, coordinated, integrated, and comprehensive care [174].*

This pivotal role is all the more crucial in diffuse, evolving pathologies such as Long COVID, which require active listening, an explicit acceptance of uncertainty, and an ability to navigate among specialties without losing the thread of clinical meaning. The general practitioner thus becomes a translator [175], in the sense evoked by Umberto Eco in *Dire presque la même chose (Mouse or Rat?)* [176], where translation is always an unavoidable negotiation between precision and loss of meaning, between specialized knowledge and patients' lived experience, between scientific uncertainties and concrete needs.

This stance aligns fully with the logic of quaternary prevention [177], which from its inception positioned itself at the confluence of the medical discourse (seeking *diseases*) and the patient's discourse (expressing *illness*): a critical attitude toward overmedicalization, ethical vigilance against iatrogenic risk, and constant attention to do no harm (principle of nonmaleficence), even with the best intentions. In the context of Long COVID, quaternary prevention urges us not to reduce complexity to default categorical psychiatric diagnoses, not to disqualify lived experience and complaint, and to support patients through their journeys of wandering and recognition. It restores medicine's fundamental protective role (principle of beneficence): to care, amid uncertainty, with prudence, listening, and humility [178].

A medical education that is insufficiently reflective and in need of reconfiguration

> *In April, I went back to my doctor because I was really very, very tired, and that's when he took me off work again.*
> *So, was the diagnosis Long COVID or not?*
> *No, at that point, since at the beginning we hadn't really pinpointed Long COVID, the doctor wrote depressive disorder... For the extension, he kept the same thing for fear that the mutual insurance would send me back to work. Ah no, he wrote mixed anxiety–depressive disorder.*
>
> — M. Jamoulle, consultations, 2025

The training of caregivers—physicians in particular—remains largely built on a transmissive model focused on accumulating factual knowledge and repeating standardized protocols. This model, inherited from a positivist, hospital-centered tradition, tends to privilege memorization and conformity at the expense of critical thinking, clinical uncertainty, and contextual analysis. Students are rarely encouraged to question how knowledge is constructed, to examine diagnostic gray zones, or to open up to interdisciplinary approaches.

This culture of reproduction—sometimes reinforced by highly standardized assessment mechanisms—limits future physicians' ability to address complex, emerging, or poorly understood situations like Long COVID. It also slows recognition of experiential knowledge, especially that borne by patients. In this context, medical education inadvertently contributes to the marginalization of so-called "invisible" or "non-objectifiable" conditions.

To address these limits, many voices call for deep pedagogical reform. One of the most explored avenues is the introduction of Problem-Based Learning (PBL), developed notably at McMaster University in Canada in the 1970s [179]. This method places students in active, group-based resolution of complex clinical cases, without prior lectures. It stimulates critical thinking, interdisciplinary collaboration, and the dynamic integration of foundational knowledge into clinical practice [180].

Recent studies show that curricula integrating PBL foster not only better knowledge retention but also a more reflective posture open to complexity [181]. Faced with conditions as multisystem and ambiguous as Long COVID, these competencies are crucial.

Rethinking medical education thus means not only modernizing content but transforming caregivers' cognitive stance from the outset: shifting from a vertical logic of expertise to a posture of scientific humility, active listening, and shared knowledge-building.

Medical education, still largely based on the Flexnerian model [182], must be rethought. Cognitive posture should focus more on listening by teaching the caregiver–patient relationship and qualitative inductive methodologies through immersive modules introduced early in medical studies [183]. Room must be made for anthropology, recalling that the practicing physician is an anthropologist in their own way, who must first immerse themselves in the patient's world through attentive listening and specific questioning [184] rather than forcing a fit into pre-established diagnostic categories.

Patients in a position of epistemic inferiority and the emergence of a collective voice

Patients traditionally occupy an inferior position in the care relationship, insofar as they present as requesters. Their words are often considered emotional, subjective, or

insufficiently credible compared to medical knowledge validated by science. They may be poorly formulated: either obvious and too quickly "understood," or less clear—and that is when the true communication problem arises. Reluctant to contest medical authority, especially in vulnerable situations, patients become exposed to misleading messages—issued, consciously or not, by professionals themselves [145]. This epistemic imbalance is particularly marked in Long COVID, where the absence of biomarkers and normal test results reinforce the disqualification of patients' narratives. Consequently, this situation restores the full dimension and value of the medical history.

However, this asymmetry of knowledge has been powerfully challenged by the irruption of patients themselves into the public and scientific sphere. It was in fact the patient community—and not the medical world—that coined the term *Long COVID*, as early as May 2020, on social networks [185]. Faced with institutional inaction, patients worldwide—often with academic, healthcare, or activist backgrounds—organized into collectives, conducted surveys, built databases, produced guides, and even published in peer-reviewed journals. This unprecedented reversal of traditional roles makes Long COVID one of the most striking contemporary examples of *patient-led research*.

Patient associations—such as *Long COVID Support* (United Kingdom), *Body Politic* or *Long COVID Foundation* (United States), *Long COVID Belgium*, or *ApresJ20* (France)—have played a decisive role in raising visibility, securing institutional recognition, structuring care demands, and promoting interdisciplinary research centered on patients. Their action has been essential not only in bringing forth the diagnostic category but also in compelling health authorities to take a stand.

In this sense, Long COVID exemplifies a contemporary dynamic in which patients are no longer merely subjects of care but *agents of knowledge* and drivers of health-system transformation.

Between institutional mistreatment and reductive simplification

The situation of children and adolescents with Long COVID is particularly alarming [186]. Their symptoms—often invisible to standard tests—are minimized or even denied by caregivers and school institutions. Due to the lack of recognition of pediatric Long COVID, these children are suspected of malingering or school avoidance, and their families of overprotection or encouraging complaints [187]. This double disqualification—medical and educational—exposes some to real situations of institutional mistreatment [188, 189]: refusal of accommodations, default psychiatric referrals, unjustified reports. It is essential that public health institutions, mutual insurers, schools, and employers be sensitized to the impact of Long COVID on individuals' real functional capacity. Supporting adaptations in pace, expectations, and modes of work/study becomes a health and social priority.

This reflex of clinical disqualification is part of a tradition of marginalizing "medically unexplained" complaints. It is aggravated by the radical novelty of Long COVID, whose symptoms confound usual diagnostic frameworks. Lacking appropriate tools, caregivers too often resort to psychiatric labels by exclusion, at the expense of listening-centered care.

The Dunning–Kruger effect and meta-ignorance

This reductive reflex can be read in light of the Dunning–Kruger effect [190]: professionals with low competence on the topic, due to lack of training or interest, overestimate their ability to judge the pathology. They thus hastily conclude that there is no disease,

without recognizing the limits of their own understanding.

To this is added a more insidious form of meta-ignorance: not only do some actors not know, but they do not know that they do not know [191]. This double layer of unrecognized and unquestioned ignorance makes recognition of Long COVID particularly difficult. It has recently been described as an aggravating factor in public health policy when it impedes perception of collective risk [192].

A medicine still blind to gender

Finally, gender is crucial. Long COVID predominantly affects women—often young, active, and previously healthy. This female prevalence, well documented in the scientific literature, highlights a structural bias in contemporary medicine, which remains largely androcentric [193]. Women's complaints—diffuse pain, chronic fatigue, cognitive disorders, dysautonomia—have historically been taken less seriously, frequently attributed to psychological or hormonal causes, or dismissed as supposed emotional hypersensitivity.

In the context of Long COVID, this gender bias manifests as a tendency to minimize symptoms, delay specialized testing, or refer women to psychiatric consultations without thorough somatic exploration. This phenomenon fits within a systemic pattern of discrediting female patients, well known in chronic "invisible" diseases (fibromyalgia, endometriosis, chronic fatigue syndrome). As Woitowich et al. emphasize, the chronic underinvestment in biomedical research on conditions that preferentially affect women contributes to persistent inequalities in care [194]. Long COVID sadly aligns with this pattern.

Political inertia in the face of a silent health emergency

To these factors is added troubling political inaction in many countries. Although evidence is accumulating on the prevalence, severity, and chronicity of Long COVID, institutional responses struggle to cohere. This gap is all the more alarming given the major economic consequences of the disease: prolonged work stoppages, professional disinsertion, increased disability claims, strain on health insurance systems, and overload of primary care.

As Gandjour notes, costs induced by Long COVID—direct and indirect—are likely to exceed those of the acute phase due to their durable, multifactorial, and hard-to-reverse nature [195]. This is therefore not only a medical or epidemiological issue but a macroeconomic and organizational challenge for health systems.

Yet in most countries, measures remain embryonic: lack of administrative recognition of the diagnosis, absence of coordinated care pathways, delays in research funding, and a statistical vacuum on real prevalence. In Belgium, although the national insurer has organized access to care, neither information dissemination nor training for frontline actors has been implemented by academic or political authorities. This inertia is aggravated by marked institutional fragmentation between levels of power (federal, community, regional), rendering health governance ineffective, even inoperative. This structural complexity fuels a sense of abandonment among patients and growing helplessness among health professionals facing a pathology they can neither diagnose easily nor steer through a stable care pathway.

In Switzerland, recommendations for treating physicians were developed by expert consensus [196] for assessments for disability insurance, based on a detailed description of functional limitations rather than a categorical diagnosis. These recommendations concern functional disorders such as chronic pain or fatigue, to which Long COVID is

assimilated. In the Netherlands, the establishment of expertise centers in each province constitutes an organizational response aiming to structure the care offer [197]. Europe, too, remains behind—both in acknowledging the scale of the phenomenon and in structuring a concerted response. The result is systemic disorganization, where political non-recognition feeds medical non-recognition, closing a vicious circle of denial, delay, and unaddressed suffering.

A systemic revealer and an opportunity for transformation

> *Most commentators acknowledge that standardization is a powerful process. Used well, it promises to make medicine more accessible, more cost-effective, and more democratic. But if misused, it risks stifling creativity and turning health care into a bureaucratic straitjacket.*
>
> *— Stefan Timmermans and Marc Berg. The Gold Standard: The Challenge of Evidence- Based Medicine. Temple University Press, 2010 [198].*

Thus, Long COVID acts as a revealer of structural vulnerabilities at every level of the health system and beyond. It embodies the complexity of a pathology at the crossroads of biomedical sciences—in full transformation—social power relations, gender inequalities, and institutional and political inertia. Its symptomatic polysemy, unpredictable chronicity, and interindividual heterogeneity make it a condition that eludes the classic frameworks of evidence-based medicine, standardized diagnosis, and targeted treatment.

But beyond the medical and organizational challenge it represents, Long COVID offers a unique opportunity to probe our health epistemologies in depth. It invites us to rethink how we train caregivers, how we listen to patients, and how we build—or neglect—care pathways. It compels us to move beyond disciplinary silos and to integrate cross-cutting, interprofessional, and participatory approaches.

Finally, it confronts us with a fundamental ethical question: what becomes of medicine when it is destabilized by a disease it does not yet understand? Far from being only a medical object, Long COVID constitutes a *total social fact* in the Maussian sense [199]: it engages biology, economics, politics, social norms, and our very relationship to knowledge, vulnerability, and recognition. This global, systemic dimension echoes other health crises such as HIV, where the medical field was confronted with unprecedented forms of suffering, contestation, and reconfiguration of medical knowledge [200].

What stance/posture should the caregiver adopt in practice?

> "The knowledge of reality is a light that always casts some shadows. It is never immediate and complete. It is always a correction of prior knowledge. One must therefore wipe the slate clean of what one believes one knows, and patiently regain the very spirit of science, which is a struggle against illusion."
>
> — Gaston Bachelard, *The Formation of the Scientific Mind*, 1938 [201].

Responding to the challenge of Long COVID means rebuilding trust between caregivers and cared-for, reconstructing a common language between science and clinic, and above all recognizing that for medicine to remain alive, it must be able to question itself.

Long COVID confronts us with the same uncertainty as all chronic, multisystem diseases of unknown origin. We face two possibilities:

1. We may be facing a rare disease whose scientific recognition remains incomplete. Patient associations for rare diseases often recall lengthy diagnostic wandering, sometimes resolved by the later discovery of a biological marker. One in seventeen people is likely to be affected by a rare disease during their lifetime, implying that general practitioners will encounter such patients regularly [202]. This observation urges continued investigation and warns against prematurely closing diagnostic options through reductive psychiatrization [203]. The psychiatric label indeed constitutes a form of reductionism, especially since it often results from observing a reactive anxiety–depressive state due to the cumulative impact of illness and the lack of recognition accompanying it.
2. We may be facing a complex disease with bio-psycho-social determinants, and for such conditions the deleterious effects of endless investigations are well known, as they sidestep the narrative and subjective dimension of suffering by answering "beside the point." The general practitioner must not lose their role as translator [175], enabling the patient to work through their suffering even when this is difficult.

How should one position oneself in the face of such a dilemma: remaining faithful to Balint's legacy [204] while staying open to scientific advances? This stance requires a true balancing act. Following the teaching of Gaston Bachelard [201], who inventoried the obstacles to scientific knowledge at the turn of the 18th and 19th centuries—showing how images, analogies, and metaphors can block understanding—we must undertake the same effort of *psychoanalysis* today, in an era when the biomedical model triumphs.

The latter proposes a new metaphor: that of a rational, categorical world comparable to a computer program, where standards are elevated to untouchable truths [198], leaving little room for the patient's singular voice.

We have attempted to identify these new obstacles. They can be overcome through a discipline of mind based on the constant testing of acquired knowledge, its correction, and even rupture—thus defining the family physician's ethical posture in the face of uncertainty:

— Intellectual and affective catharsis obliges us to reflect and to be clear-eyed about our defensive medical tendencies [205].

— Reforming our mindset will bring us to a more inductive stance, listening to the patient, becoming anthropologists in our own way [184].

— Rejecting the argument from authority implies the postulate of sincerity [206]: the patient must be believed; otherwise, we practice military medicine in search of malingerers—which is no longer general practice.

— Commentators on Bachelard add that we must keep our reason unsettled and continue to ask questions. This is, moreover, Sackett's original position as the creator of evidence-based medicine.

— Since it is impossible to define what we do not yet know, it is essential to return the floor to patients. When rigorously collected and structured, that speech constitutes a biological fact in its own right. Organized coherently, it can become a terminological biomarker [207].

Faced with a patient who *has nothing* on test results but *can no longer live as before*, it is essential to suspend judgment, listen actively, and acknowledge that our science does not yet know everything. Failing to recognize Long COVID adds medical violence to suffering. The physician's role is not only to diagnose what is visible but to accompany what is invisible.

In plain language

Long COVID: a new disease confronting a destabilized medicine Long COVID profoundly disrupts our health system. Despite thousands of published studies, many physicians remain in the dark. Patients feel abandoned, disbelieved, sent from one consultation to another without answers. A fracture has opened up: between patients and physicians, and also between physicians and scientists.

Why? Because Long COVID is a new disease, unlike what medicine is used to. It affects memory, concentration, language, the nervous system, and blood vessels—and often, especially women. Exams are often normal, but the suffering is very real.

This situation reveals several problems:

— Medicine too centered on technology and organs, not enough on the person.

— Medical training that is insufficiently critical, where one learns to repeat rather than to think.

— An influence of the pharmaceutical industry that is too strong on medical information.

— A lack of political response, despite the massive social and economic consequences of Long COVID.

Long COVID shows how much medicine and society must evolve. It is a challenge—but also an opportunity to rethink how we care, listen, and understand.

3.16 Perspectives from Other Belgian Physicians in the Long COVID Network

The Long COVID Research Network was formed progressively, in the absence of effective coordination by public authorities. It was the patients themselves—faced with lack of awareness and at times denial of their lived experience—who took the initiative to connect health professionals attentive to their accounts. Thanks to this grassroots dynamic, a few physicians gradually became involved in the exchanges. Little by little, colleagues sensitive to the reality of Long COVID sought to take part in the network's discussions and work.

3.16.1 Long COVID and chronic pain: a new reality in the clinic

By Bernard Vanderick, MD, Pain Anesthesiologist, Clinique St Anne St Rémi, Brussels

Since the emergence of Long COVID, pain clinics have seen a growing number of patients presenting with recently developed chronic pain with atypical characteristics. These complaints—one of the most important symptoms of Long COVID [208]—differ markedly from those classically encountered in chronic pain syndromes: their narrative, topography, and evolution do not follow usual patterns, making diagnosis difficult and therapeutic choices uncertain.

The clinical pictures reported include persistent headaches, non-systematized neuropathic-type pain, diffuse myalgias, and arthralgias. These painful symptoms often occur in a context of global deterioration of general condition, with a significant impact on quality of life. In some cases, they represent decompensation in patients already known for chronic pain. However, for a great many of them, these are de novo painful symptoms that appeared in the wake of a SARS-CoV-2 infection.

Early epidemiological data report an incidence of post-COVID chronic pain ranging from 15 to 45%. A study published in 2023 by Gabriel T. Kubota and Felipe H. C. Soares specifically analyzes the onset of new chronic pain after a COVID-19 infection [209]. The authors identify different pain phenotypes, notably musculoskeletal and neuropathic pain. These pains are frequently accompanied by fatigue, sleep disorders, anxiety, and depressive symptoms.

The pathophysiology of these manifestations remains poorly understood. Several hypotheses are discussed, ranging from persistent inflammatory processes to multisystem tissue involvement. Based on current knowledge, it would be premature to assimilate these presentations to other well-described entities such as fibromyalgia or chronic fatigue syndrome. It should also be recalled that chronic pain is a complex experience, both sensory and emotional. This dual component implies that the pain experience partly depends on the patient's subjective life and cognitive mechanisms [210].

The emotional aspect of pain—particularly plastic—can foster chronicity, notably when it coexists with fatigue, anxiety, or sleep disorders. Management of these patients is therefore particularly complex. It requires a multidisciplinary approach focused on physical symptoms, psychological distress, and functional limitations alike. However, this clinical reality remains insufficiently recognized, due to diagnostic difficulty and the absence of consensual criteria for characterizing these post-COVID pain syndromes.

3.16.2 Experience at Ath Hospital

Paul Thielemans, internist, Hôpital d'Ath, Belgium

Certain observations from my hospital experience may help enrich understanding of the clinical picture of Long COVID. These findings come from a series of about 80 patients seen at Ath Hospital between late 2022 and early 2025, as part of occasional specialized consultations, without a true longitudinal follow-up.

The complaints expressed by patients share several striking features. First, the chronology of symptoms is often puzzling: no clear trigger at onset, unpredictable timing and duration, marked fluctuations with periods of improvement followed by unexpected relapses. These variations mainly concern fatigue, headaches, and limb pain.

Second, the complaints often elude classical nosological frameworks. For example, headaches do not fit usual classifications, and limb pain is not accompanied by joint inflammatory signs (redness, edema) nor by clear neurological signs suggesting polyneuropathy. It is also common to observe reactivation of old pains predating the initial infection, giving the impression that Long COVID acts as a painful reminder: "it presses where it hurt or had hurt" [140].

Progression to chronicity is often associated with a secondary anxiety–depressive state, whose intensity varies among patients but contributes to the complexity of the overall clinical picture [141].

Regarding work incapacity, a notable feature is the strong motivation of patients to return to their activities. This will appears spontaneously, with concrete attempts at professional reintegration, unfortunately often followed by failures [142].

These observations were collected in a particular framework: not being in a position nor authorized to substitute for the treating general practitioner, the consultations were limited to occasional evaluations prompted by tests, administrative processes (incapacity certificates), or the patient's own request.

It was therefore not a continuous management. Nonetheless, these clinical stories confirm existing descriptions in the literature [143] and illustrate the distress of patients faced with the lack of a structured response, despite efforts deployed by the INAMI.

The objectives of this consultation opened in late 2022 were several:

1. identify overlooked or underestimated diagnoses (asthma, iron deficiency, diabetes) [148];
2. provide a structured medical report, useful for memory, understanding, and administrative processes;
3. establish a patient registry for research purposes;
4. organize a monthly multidisciplinary meeting (GPs, specialists, allied health). This initiative failed after two quarters, except for a few fruitful collaborations (occupational therapy, neuropsychology, social work) and rare exchanges with treating GPs.

3.16.3 A Long COVID clinic at Clinique Saint-Luc de Bouge, Belgium

Dr. Jean-Baptiste Nicolas, general internist

The COVID-19 pandemic arrived like a tidal wave, overwhelming health care from the beginning of 2020. Barely had this global crisis stabilized when another form of pandemic emerged: Long COVID—more insidious, harder to grasp.

Initially perceived as a simple post-infectious recovery phase, it proved to be a chronic, unexpected, persistent condition. Patients—often young, active, and previously healthy—saw their daily lives upended. The slightest effort, physical or intellectual, became exhausting. The majority found themselves on prolonged sick leave. The socioeconomic impact is considerable.

Gradually, health professionals recognized the scale of the phenomenon. More than 200 symptoms have been identified to date, some very frequent: fatigue (98%), post-exertional malaise (89%), cognitive disorders or "brain fog" (85%), dyspnea, dysautonomia (POTS, orthostatic hypotension, imbalance, digestive disorders), anxiety–depressive affect [**davis2023longCOVID**, 211].

This protean, non-specific symptomatology has unsettled the medical profession. These patients did not fit classic classifications and were too often redirected to psychiatric consultations.

Fortunately, science has advanced: studies show a very real pathophysiology, including immune dysregulation, neuroinflammation, endothelial dysfunction, microthromboses, viral persistence, dysbiosis, autoimmune phenomena, and immune priming [212, 213].

My clinical practice was profoundly disrupted. In 2021, I began seeing a few patients with post-COVID complaints. Their specialized tests were normal, but symptoms persisted. As I read up, I noted striking similarities with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), both clinically and physiopathologically [213].

With no established protocol, management was initially very empirical. Apart from some advice on pacing, gentle reconditioning, and psychological and neuropsychological support, we were at a loss. Validating symptoms constituted an ethical and clinical foundation. Drawing on the scant EM/CFS data and early Long COVID recommendations, I prescribed, according to each patient's profile, treatments aimed at reducing neuroinflammation, improving cerebral perfusion, regulating neurotransmitters, modulating dysautonomia, with occasional neuromodulation approaches. I also emphasized hygiene–dietary measures, gentle physical therapy, cognitive rehabilitation, and psychological support. Some patients improved, but word of mouth quickly overwhelmed my clinic: delays jumped from 3 to 6 months in weeks. I now follow 300+ Long COVID patients, many developing ME/CFS, chronic pain, or dysautonomia, forcing me to reorganize my practice.

Individual efforts are insufficient. Belgium's national insurer INAMI is rightly considering multidisciplinary centers for post-infectious syndromes—an urgent need. Long COVID is a disabling biological reality: we must validate patients, structure care, and respond collectively and compassionately.

Chapter 4

Discussion

By Marc Jamoulle

Our research network, born in family medicine and structured around an informal partnership between clinicians, patients, and scientists, implemented an integrated approach combining clinical observations, multi-omics analyses, functional imaging, and social sciences to document and better understand Long COVID.

4.1 Genesis of the Long COVID Research Network

Clinical uncertainty is a core competency of general practitioners, accustomed to accompanying patients in situations where the diagnosis is not immediately evident. The repetition of cases presenting a set of persistent and unknown symptoms highlighted this competency while underscoring the need for deeper exploration.

It is in this context that an original action-research project emerged. A bridge was established between primary care and scientific research, giving rise to the *Long COVID Research Network*. Thanks to pre-existing contacts with genetics teams, this informal network rapidly became international, establishing links between Belgium, France, Sweden, and Switzerland. It developed on the margins of institutional transnational programs, without dedicated funding, but with a shared determination: to understand and document Long COVID by articulating daily clinical practice, biomedical sciences, and social sciences.

4.2 Assessment tools

In 2021, scales and tools specifically designed for Long COVID were still underdeveloped. We chose to use instruments already validated in family medicine, such as the *DUSOI* (Duke Severity of Illness Checklist) and the *COOP/WONCA Charts*. These tools have the main advantage of offering a global approach to health status, integrating clinical, functional, and subjective dimensions.

The *COOP/WONCA Charts*, for example, take two to three minutes to administer, do not require literacy, are readily grasped by patients, and yield results comparable to more complex quality-of-life tools [214]. Their simplicity and low cost in time and resources make them well-suited to the front line.

Many studies have since analyzed the impact of Long COVID with similar tools, sometimes focused on specific dimensions such as fatigue [215, 216]. Our choice reflects a pragmatic approach, favoring a global view of the patient's health rather than an isolated

measure. Newer, more targeted instruments are now available [217] or under validation, including for children [218, 219].

4.3 Use of large language models (LLMs)

Large language models (LLMs), such as ChatGPT, offer novel prospects for structuring clinical narratives and supporting diagnostic reasoning in Long COVID. A systematic review of more than 760 studies highlights their potential in diagnosis, education, and clinical decision-making [220], while others point out their current limitations (risk of bias, lack of standardized evaluations, "hallucination" errors) [221].

In comparative studies, LLM assistance improves diagnostic accuracy by establishing complex differential diagnoses [222]. Their use could therefore enrich symptom analysis and standardize narratives via frameworks like HPO. However, their role must remain complementary to the empathetic, contextualized human expertise of general practitioners.

4.4 Biological signatures and viral persistence

The biological signatures identified by our network (transcriptomic, proteomic, immune) support the hypothesis of viral persistence, already raised by several international studies. The partial reversibility observed with antivirals reinforces this hypothesis, but controlled trials are needed.

Recent experimental data confirm this perspective: at the Institut Pasteur, persistence of SARS-CoV-2 was demonstrated in the brainstem of hamsters up to 80 days after infection, with the presence of viral RNA and proteins [26]. These results support the idea of an active viral reservoir that may contribute to chronic symptomatology.

4.5 Neuroimaging and biochemical biomarkers

Functional neuroimaging and biochemical biomarkers reveal metabolic and vascular disturbances invisible to standard tests, suggesting persistent involvement linked to symptoms. Their place in clinical practice remains to be defined, given costs and availability.

It should be emphasized that in Belgium, despite numerous efforts, it was not possible to perform functional MRIs, which are more accessible in France. This disparity illustrates inequalities in access to cutting-edge diagnostic tools.

4.6 Contributions of the social sciences and history-taking

The social sciences highlight an epistemic imbalance: in the absence of established biomarkers, patients' narratives are often disqualified, fueling diagnostic wandering and psychologizing explanations. International qualitative research has precisely documented the suffering related to Long COVID and its social consequences [223, 224].

In Belgium, a qualitative survey was initiated in 2021 but could not be continued due to lack of resources. This shortfall limits the integration of lived experience into research, even though it is an essential source of knowledge.

4.7 Terminology in the service of patients

The use of the *Human Phenotype Ontology (HPO)* illustrates the value of a standardized clinical terminology in the direct service of patients. It makes it possible to transform narratives into a standardized language, facilitating their integration into biomedical research and contributing to the recognition of lived experience.

Other applications of ontologies have shown their relevance in psychiatry [225], in narrative medicine [226], and in differential diagnosis [227]. Thus, far from being an administrative tool, terminology becomes an instrument of recognition and diagnostic precision.

4.8 Strengths and limitations of the approach

The multidisciplinary approach demonstrates its strength by cross-referencing molecular, clinical, and social data. But it confronts the difficulty of integrating heterogeneous information into daily practice.

A specific feature of this study lies in the fact that the clinical work was carried primarily by a single front-line physician. This singularity is a strength (continuity, coherence, deep knowledge of trajectories) but also a weakness (risk of bias, limited reproducibility).

The absence of funding and logistical structures underscores the fragility of a model based on individual commitment. To sustain these advances, institutional, financial, and collaborative foundations will need to be reinforced.

4.9 Comparison with the literature

As early as 2021, several international guidelines were published to guide family medicine [228, 229, 230]. In 2023, a retrospective study of English GP records confirmed the multisymptomatic nature of Long COVID [231]. The *Patient-Led Research Collaborative* published convergent data from thousands of patients [232].

Approaches based on natural language processing in primary care were already in place before the pandemic and proved relevant for Long COVID [233].

Our study cannot compete with the large-scale, federally funded RECOVER cohort in the United States [234], but our results largely converge, confirming Long COVID as a chronic, multisystemic, and persistent disease.

Unlike other countries where networks were initiated by public authorities and centered on hospitals, our approach is bottom-up, rooted in primary care and built with patients. It demonstrates that family medicine can be a driver of innovative research, directly linking clinical experience with high-level science.

One of the main challenges encountered over the course of this research lies in the progressive accumulation of data. At the launch of the study, nothing suggested that within four years, the number of included patients would reach 320. While data collection was carried out systematically, the entire cohort could not be reviewed. Due to limited financial resources, it was not possible to mobilize the personnel needed for in-depth analysis of this corpus. Without additional funding, there is a real risk that these valuable data will remain unexploited and feed what could become a "data graveyard."

4.10 Recording consultations: ethical issues and clinical impacts in the context of Long COVID

A clinical use, not an *a priori* research endeavor

In the case at hand, recording is not used for a conventional research purpose. It falls within the practice of family medicine in Belgium, in a therapeutic relationship engaging physician and patient. The physician, responsible for the electronic medical record, ensures that collected data are integrated into this record, to which the patient may have access.

Thanks to current technologies, notably the use of a smartphone, recording the patient's speech becomes seamless. It captures a narrative that is often complex and hard to structure in the flow of the interview.

Transparency and collaboration

Recording is always performed with the patient's explicit consent, who can follow in real time, on the physician's screen, the automatic transcription of their statements, in French. This transcription, visible, reread, and corrected, is integrated into the designated application. This process reveals a new structuring of complaints and enables the patient to perceive the reality and coherence of their illness.

An emerging therapeutic function

This is not only about extracting data for analytical purposes, but about co-constructing with the patient a clear representation of their lived experience. This work often helps to move beyond the paradigm of the "invisible illness," where everything is felt but nothing is objectified. In this context, recording becomes a tool of quaternary prevention [21]. It helps the physician pull the patient out of this diagnostic "black hole," where everything is felt but nothing is objectified. Tests are normal, imaging is noncontributory, and doubt sets in. This is precisely where family medicine has a key role to play: revealing, with the patient, the extent and coherence of their symptomatic experience.

A strong ethical anchor: the Cos Declaration (1992)

This clinical posture fully aligns with the principles set out in the Cos Declaration (1992) [235], developed by European health professionals committed to a humanistic medicine. This declaration affirms unconditional respect for the sick person, the legitimacy of all forms of suffering, and the importance of co-constructing care. It invites us to walk "side by side" with the patient, to reject any symbolic or technical violence, and to acknowledge the uncertainties of science without obscuring the reality of emerging pathologies. In the context of Long COVID, these principles take on particular urgency. They call for hearing what patients live, welcoming their narrative in its complexity, and offering them a space of recognition. When integrated judiciously, the technological use of recording thus becomes a tool in the service of an ethics of relationship, speech, and recognition.

Inform, accompany, recognize

Once this work is done, the physician's role is twofold: both to inform the patient of the current limits of medical knowledge—particularly around Long COVID—and to

help them recognize that they have a chronic illness, often invisible but disabling. This disease profoundly affects cognitive, physical, and emotional functions, as well as the very organization of daily life. The patient is moreover confronted with a double negation: that of the illness—because it is not visible—and that of their own existence as a suffering subject, called into question by some health professionals.

We are far removed here from quantitative research applied to anonymous cohorts. This is a deeply personalized approach, embedded in a care relationship. In this setting, the requirement of formal signed consent becomes secondary: the patient is present, active, engaged in the exchange. As long as the data remain within the confidential framework of the medical office and the electronic record, their use complies with professional secrecy.

Chapter 5

Conclusion

A Participatory Action Research Approach

The activities presented here are part of a participatory research process in which patients' experiential knowledge plays a central role. The clinic—an arena of listening, relationship, and the intelligibility of suffering—serves both as the entry point and the guiding thread. Patients' narratives, lived experiences, and biological data inform the investigations carried out by teams confronting the complexity of conditions caused by SARS-CoV-2. Patient experience is not only the starting point of the research but also its framework throughout the process of knowledge production.

Key Findings

- Building a bridge between primary care and cutting-edge multidisciplinary research is both *feasible* and productive.
- Clinical practice makes it possible to identify, name, and document the disease, as well as to articulate suffering.
- Partnership with patients guides and shapes the research.
- Advanced molecular biology tools enabled large-scale screening of fluids to search for biomarkers and evidence of viral persistence.
- Transcriptomics detects RNA, including antisense sequences, long after acute infection, suggesting the existence of viral reservoirs.
- Proteomics shows that, in some patients, viral proteins persist for months after infection.
- Neurobiology suggests an immune-mediated mechanism of pain (transferable via IgG in mice).
- Immune profiling is *consistent* with the viral hypothesis (prolonged activation, altered T-cell responses).
- Genomics explores susceptibility factors, though findings are emerging more slowly.
- Advanced brain imaging reveals perfusion abnormalities and/or metabolic and neuro-inflammatory signatures not visible in standard exams.
- Qualitative research sheds light on the distress and disruption of life caused by the disease.
- The health system has responded inadequately: lacking guidelines, fragmented services, and insufficient structures.
- A divide persists between patients and physicians, as well as between clinical medicine and science.

This report attests to the emergence, within general practice, of a chronic, multisystemic, and disabling post-viral condition with fluctuating manifestations: Long COVID. The interdisciplinary and participatory approach of the Long COVID Research Network moves beyond the limitations of strictly "top-down" biomedical objectification by integrating the contributions of patients, clinicians, and laboratory teams. The use of the *Human Phenotype Ontology* (HPO), detailed analysis of patient narratives, and openness to omics and digital humanities point toward the recognition of Long COVID as a medical entity, while proposing a model of research anchored in the realities of care.

Recommendations It is now urgent that Belgian and European authorities recognize the scope of this silent health crisis. We call for:

- ⋆ the **official recognition of Long COVID** as a systemic chronic disease, with a dedicated nomenclature, structured care pathways, and facilitated access to multidisciplinary expertise;
- ⋆ the **creation of cross-cutting reference centers**, connected to primary care and equipped with appropriate human, technical, and digital resources;
- ⋆ a **sustainable public investment in research**, targeting biomarkers, diagnostic tools, and evaluation of personalized treatments;
- ⋆ **proactive integration** into European initiatives (EHDS, CHGE, Horizon Europe), ensuring Belgium contributes fully to collective efforts;
- ⋆ and finally, a **renewed ethical foundation for the patient–provider relationship**, centered on recognition of lived experience, reducing medical wandering, and establishing quaternary prevention as a public health imperative.

Long COVID is not an epidemiological anomaly but a warning sign of our capacity to think, listen, and provide care over the long term. In the era of digital health, precision biology, and citizen participation, policymakers must engage lucidly with this transformation.

List of Figures

Liste des acronymes

ACE2 ; Angiotensin-Converting Enzyme 2

ASBL ; Association Sans But Lucratif

AVAI ; Années de Vie Ajustées sur l'Incapacité

AVIQ ; Agence pour une Vie de Qualité (Wallonie)

BPCO ; Bronchopneumopathie Chronique Obstructive

CDC ; Centers for Disease Control and Prevention

CDM ; Common Data Model (modèle commun de données)

CHGE ; COVID Human Genetic Effort

CHU ; Centre Hospitalier Universitaire

COOP/WONCA ; COOP Charts — World Organization of Family Doctors

COVID ; Coronavirus Disease

DMI ; Dossier Médical Informatisé

DALY ; Disability-Adjusted Life Year (équivalent AVAI)

DUSOI ; Duke Severity of Illness Index

EHDS ; European Health Data Space

EGPRN ; European General Practice Research Network

FWO ; Fonds voor Wetenschappelijk Onderzoek (Flandre)

FNRS ; Fonds National de la Recherche Scientifique (Belgique)

FDG ; Fluorodésoxyglucose

fRMN ; Functional Magnetic Resonance (Fr. « IRM fonctionnelle »)

HPO ; Human Phenotype Ontology

ICPC-2 ; International Classification of Primary Care — 2^{e} révision

ICPC-3 ; International Classification of Primary Care — 3^{e} révision

INAMI ; Institut National d'Assurance Maladie-Invalidité

KCE ; Centre fédéral d'expertise des soins de santé (Belgique)

LLM ; Large Language Model

ME/CFS ; Encéphalomyélite myalgique / Syndrome de fatigue chronique

NASEM ; National Academies of Sciences, Engineering, and Medicine

OMOP ; Observational Medical Outcomes Partnership

ORDO ; Orphanet Rare Disease Ontology

PET ; Positron Emission Tomography

POTS ; Syndrome de tachycardie orthostatique posturale

PROMs ; Patient-Reported Outcome Measures

RECOVER ; Researching COVID to Enhance Recovery

RGPD ; Règlement Général sur la Protection des Données

RSW ; Réseau Santé Wallon

SARS-CoV-2 ; Severe Acute Respiratory Syndrome Coronavirus 2

SNOMED CT ; Systematized Nomenclature of Medicine — Clinical Terms

ULB ; Université Libre de Bruxelles

ULg ; Université de Liège

UCLouvain ; Université catholique de Louvain

UZ ; Universitair Ziekenhuis (hôpital universitaire, NL)

Zotero ; Logiciel libre de gestion bibliographique

Chapter 6

Appendices

6.1 Anonymized Report

Dr. Jamoulle, April 5, 2025
Reproduced with the formal authorization of the parents and the young woman.
To the attention of the primary care physician

Patient: 16 years 9 months — Female

Dear Colleague,

Your patient consulted me with her parents for an opinion on her clinical condition. She is a 16-year-old adolescent followed for severe post-infectious symptoms that appeared after a pulmonary COVID episode in May 2024. She presents multisymptomatic neurological involvement, major chronic fatigue, sensory disturbances, signs of dysautonomia, and significant cognitive and functional impairment.

Clinical history and symptomatology

April–May 2024: post-infectious onset

— Acute febrile respiratory infection (38,6℃), suspected bronchitis without PCR confirmation.

— Pulmonary COVID confirmed in May.

— Symptoms: persistent diffuse headaches, fatigue upon awakening, nocturnal low-grade fever, cough, recurrent sore throat.

June–October 2024: complex neurological episodes

— Holocranial headaches, moderate photophobia.

— Paroxysmal episodes: nausea, tremors, hyperventilation, altered consciousness, dysarthria, hypersalivation, transient visual disturbances, postictal ataxia.

— Normal brain MRI (07/17/2024); epilepsy excluded (10/15/2024); follow-up EEG pending.

— Brufen (ibuprofen) effective for pain.

September 2024: functional decline

— Complete withdrawal from school due to disabling fatigue.

— Altered functional status: cannot sustain continuous cognitive or physical effort.

— Unable to follow remote classes.

Detailed neurological and cognitive symptoms

Cognitive and executive dysfunction

— Impaired reading comprehension: reading is possible but comprehension is altered, requiring multiple rereads of the same passage.

— Impaired immediate memory: frequent forgetting of recent events; difficulty recalling simple activities (e.g., weekend schedule).

— Preserved declarative memory: previously acquired knowledge retained (e.g., school knowledge).

— Fluctuating cognitive impairment: phases of mental disorganization, especially upon waking.

Language and memory functions

— Episodic dysarthria with altered prosody, high-pitched voice, slowed speech.

— Mismatch between word read and word spoken: incorrect or unrecognized words, semantic errors.

— Difficulties with calculation: fluctuating deficits, sometimes unable to solve simple problems.

Behavioral disturbances

— Inappropriate laughter, giggling out of context (e.g., during a family meal), incongruent with baseline temperament.

— Behavioral changes: social withdrawal, emotional hypersensitivity, irritability.

— Mood disorder: emotional lability, frequent crying, performance anxiety.

Auditory and visual disturbances

— Severe hyperacusis: faint sounds perceived as intrusive (e.g., another person's breathing).

— Intermittent blurred vision without identified ophthalmologic abnormality.

Sensorimotor and posture

— Orthostatic intolerance: dizziness, blackout vision, sensation of falling when standing up.

— Probable orthostatic hypotension: suspected delayed vascular response.

— Transient facial asymmetry: drooping of the labial commissures during episodes or upon waking.

Sleep disturbances

— Chronic fatigue not restored by sleep, with long naps (2 to 3 hours) without restorative effect.

— Intense, realistic dreams, confusion between dream and reality.

— Frequent nocturia, nighttime awakenings to urinate, fragmenting sleep.

— Persistent daytime sleepiness, loss of attention during the day.

Follow-up and tests performed

— Normal brain MRI.

— Non-contributory laboratory tests.

— EEG planned.

— Follow-up in neurology, pediatrics, pulmonology, physical therapy.

— Psychological follow-up recommended but not initiated.

Conclusion

The presentation is compatible with severe pediatric Long COVID, with predominant neurological and dysautonomic involvement. Functional status is severely impaired, with no identified structural cause. A cardiology *tilt test* is recommended, and a therapeutic trial with ivabradine is being considered.

Recent studies support the hypothesis of persistent endothelial and microcirculatory involvement:

— Mejía *et al.* [236]: systemic vascular endothelial dysfunction.

— Hohberger *et al.* [237]: alterations of macular and peripapillary microcirculation.

— Fogarty *et al.* [238]: persistent endothelial activation and prolonged procoagulant effect.

Stroke prevention: Aspirin 80 mg daily.
Migraine management: trial of sumatriptan / ibuprofen.

Proposed management

— INAMI declaration: code 144050 to be verified.

— Requests for neuropsychological and physical therapy care.

— Treatment: Asaflow 1/day; sumatriptan on trial.

— Clinical re-evaluation in one month.

— School certificate to be discussed again.

Additional recommendations

— Regular physical and cognitive activity without overexertion.

— Use of the Neuronation app: `https://www.neuronation.com/`

— Contact with the Long COVID Belgium Association: `https://longCOVIDbelgium.be/`

Ongoing research

One of the reasons that prompted the patient to consult me is the immunological research conducted on my patients at the REGA Institute (KU Leuven). This research has already shown the persistence of viral RNA in many patients. The working hypothesis is that of a chronic, fluctuating, and disabling viral illness. The patient took home blood collection materials for transcriptomic and proteomic analyses aimed at highlighting the immune response to SARS-CoV-2 infection and possible viral persistence.

Sincerely,

Dr. Marc Jamoulle

6.2 HPO-coded Symptoms in Pediatric Long COVID

.

The following tables list all Human Phenotype Ontology (HPO) terms identified in ten children with long COVID, seen in general practice between 2021 and 2025. These detailed data complement the summary figures and tables in the main text (see Section 3.5).

HPO URI	Symptom	HPO URI	Symptom
HP:0002027	Abdominal pain	HP:0004396	Decreased appetite
HP:0004323	Abnormal sensation of body weight	HP:0000716	Depression
HP:0002360	Abnormal sleep pattern	HP:0002014	Diarrhea
HP:0041051	Ageusia	HP:0031987	Difficultés de concentration
HP:0004408	Altered sense of smell	HP:0001756	Dizziness
HP:0030840	Ankle pain	HP:0000958	Dry skin
HP:0001798	Anomia	HP:0001260	Dysarthria
HP:0002039	Anorexia	HP:0002270	Dysautonomia
HP:0000739	Anxiety	HP:0100607	Dysmenorrhea
HP:0002829	Arthralgia	HP:0002094	Dyspnea
HP:0031987	Attention deficit	HP:0030766	Ear pain
HP:0003418	Back pain	HP:0003236	Elevated serum creatine kinase
HP:0001751	Balance disorder	HP:0100851	Emotional distress
HP:0002141	Balance impairment	HP:0000712	Emotional lability
HP:0030972	Blood pressure abnormality	HP:0000458	Episodic anosmia
HP:0000622	Blurred vision	HP:0025271	Esophageal spasm
HP:5200430	Bradyphrenia	HP:0100633	Esophagitis
HP:0025289	Cervical lymphadenopathy	HP:0001262	Excessive daytime sleepiness
HP:0100749	Chest pain	HP:0003546	Exercise intolerance
HP:0031352	Chest tightness	HP:0002329	Exercise-induced sleepiness
HP:0025143	Chills	HP:4000033	Exertional dizziness
HP:0012432	Chronic fatigue	HP:0002875	Exertional dyspnea
HP:0033630	Cognitive fluctuation	HP:0030973	Exertional symptom exacerbation
HP:0100543	Cognitive impairment	HP:0001324	Faiblesse musculaire
HP:6000855	Cold intolerance	HP:0003388	Fatigability
HP:0025278	Cold sweats	HP:0012378	Fatigue
HP:0031987	Concentration difficulty	HP:0001945	Fever
HP:0002019	Constipation	HP:0002315	Frontal headache
HP:0012735	Cough	HP:0001288	Gait disturbance
HP:0012568	Dark circles under eyes	HP:0005263	Gastritis

Table 6.1 – 128 unique Uniform Resource Identifier (URI) in ten Long Covid children seen in general practice (2021–2025)

HPO URI	Symptom	HPO URI	Symptom
HP:0002020	Gastroesophageal reflux	HP:0001962	Nocturnal palpitations
HP:0003324	Generalized muscle weakness	HP:6000051	Oppression chest
HP:0002315	Headache	HP:0012670	Orthostatic dizziness
HP:0002046	Heat intolerance	HP:0001278	Orthostatic hypotension
HP:0000790	Hematuria	HP:0001278	Orthostatic intolerance
HP:0010780	Hyperacusis	HP:0012531	Pain
HP:0100786	Hypersomnia	HP:0031058	Pain-induced limitation of activities
HP:0000364	Hypoacusis	HP:0000980	Pallor
HP:0033748	Hypoesthesia	HP:0001962	Palpitations
HP:0031987	Impaired concentration	HP:0003401	Paresthesia
HP:0033051	Impaired executive functioning	HP:0003401	Paresthésie
HP:0100785	Insomnia	HP:0001701	Péricardite
HP:0002254	Intermittent diarrhea	HP:0002183	Phonophobia
HP:0000737	Irritability	HP:0000613	Photophobia
HP:0001369	Joint pain	HP:0009020	Post-exercise fatigue
HP:0030839	Knee pain	HP:0009020	Post-exertional fatigue
HP:0001328	Learning difficulties	HP:0003546	Post-exertional malaise
HP:0033688	Long-term memory impairment	HP:0032555	Pounding heartbeat
HP:0003419	Lower back pain	HP:0012532	Prolonged pain episode
HP:0002354	Memory impairment	HP:0000093	Proteinuria
HP:0012378	Mental exertion-induced fatigue	HP:0033031	Pyrexie
HP:0002076	Migraine	HP:0030880	Raynaud phenomenon
HP:0001276	Muscle hypertonia	HP:0000988	Redness of the skin
HP:0003326	Muscle pain	HP:0003546	Reduced exercise tolerance
HP:0001324	Muscle weakness	HP:6000023	Reduced physical activity
HP:0003326	Myalgia	HP:0003199	Reduced stamina
HP:0002018	Nausea	HP:0031417	Rhinorrhea
HP:0030833	Neck pain	HP:0033687	Short-term memory impairment
HP:0012393	New allergies	HP:0002791	Shortness of breath
HP:0030166	Night sweats	HP:0011703	Sinus tachycardia

Table 6.2 – Following - 128 unique Uniform Resource Identifier (URI) in ten Long Covid children seen in general practice (2021–2025)

HPO URI	Symptom	HPO URI	Symptom
HP:0007549	Skin desquamation	HP:6001127	Thumb pain
HP:0002360	Sleep disturbance	HP:0003768	Transient paralysis episodes
HP:5200310	Social withdrawal	HP:0001337	Tremor
HP:0002329	Somnolence	HP:0002354	Troubles de la mémoire
HP:0025439	Sore throat	HP:0002463	Troubles du langage
HP:0009088	Speech articulation impairment	HP:0000012	Urinary urgency
HP:0002242	Stool irregularity	HP:0002321	Vertiges
HP:0001279	Syncope	HP:0002321	Vertigo
HP:0001649	Tachycardia	HP:0000572	Visual blackout
HP:0001649	Tachycardie	HP:0000505	Visual impairment
HP:0002315	Temporal headache	HP:0001824	Weight loss
HP:0004370	Thermoregulatory dysfunction	HP:0030391	Word-finding difficulty
HP:0030811	Oral pain	HP:0030836	Wrist pain
HP:6000040	Needle-like pain	HP:0012531	Burning pain

Table 6.3 – Following - 128 unique Uniform Resource Identifier (URI) in ten Long Covid children seen in general practice (2021–2025)

HPO URI	Symptom	HPO URI	Symptom
HP:0012378	Fatigue	HP:0009020	Post-exercise fatigue
HP:0012432	Chronic fatigue	HP:0009020	Post-exertional fatigue
		HP:0012378	Mental exertion-induced fatigue

Table 6.4 – The term **fatigue** among ten Long Covid children verbalisation

HPO URI	Symptom	HPO URI	Symptom
HP:0003326	Muscle pain	HP:0012532	Prolonged pain episode
HP:0001369	Joint pain	HP:0003419	Lower back pain
HP:0002027	Abdominal pain	HP:0030840	Ankle pain
HP:0100749	Chest pain	HP:0030839	Knee pain
HP:0012531	Pain	HP:0030836	Wrist pain
HP:0030833	Neck pain	HP:0003418	Back pain
HP:0030766	Ear pain	HP:6001127	Thumb pain
HP:0031058	Pain-induced limitation of activities	HP:0030811	Oral pain
HP:6000040	Needle-like pain	HP:0012531	Burning pain

Table 6.5 – The term **pain** among ten Long Covid children verbalisation

6.3 ChatGPT Prompt — Symptom Extraction and HPO Mapping

The objective of the prompt is to ask ChatGPT to use the anonymized patient interview and the Human Phenotype Ontology (HPO) resource to identify and classify the relevant symptoms.

Title: *"Extraction → HPO"* **GPT Role**: `HPO expert`

Mission: Extract post-COVID symptoms from a free-text patient narrative, map them to **HPO terms** (English) and associated **codes**, then format per rules.

Instructions:

1. Identify all expressed symptoms.
2. Map each symptom to the **HPO term** (English) and **code** (`HP:nnnnnnn`).
3. After each HPO term, add in brackets the patient's **original wording** (verbatim, no correction).
4. Format the list:

```
HPO term (HP:code) [verbatim]; HPO term (HP:code) [verbatim]; ...
```

Constraints:

— HPO terms in English only.
— Codes strictly in format `HP:xxxxxxx`.
— Expected output = **list only** in the specified format.

Fixed metadata (for Excel export): `person1_id = MGA.34!`; `observation_period_start_date = 05/14/2025`

Source format of the text to analyze:

```
<<<
[PASTE THE PATIENT TEXT HERE]
>>>
```

Note: Minimal prompt for the symptom Excel file:

> HPO index/class. Format: *HPO Term ; URI ; verbalization ( )*. In French. Verify mapping. Excel export, 1 line, ";" as separator.

6.4 Request for Educational and Reasonable Accommodations Due to a Medical Condition

To the School Principal

Subject: Request for educational and reasonable accommodations due to a medical condition

I am the attending physician of _____, a student currently enrolled in _____ at your institution. I am writing to draw your attention to the health condition of _____, who has a disabling illness that significantly impacts attention, concentration, and overall energy reserve.
This medical condition requires specific reasonable accommodations within the student's academic pathway, including:

Adjustments to school schedule and workload:

— Reduction or reorganization of the timetable to allow rest periods adapted to the student's needs.

— Lighter homework and coursework to avoid overload that could worsen fatigue.

Exam accommodations:

— Scheduling of quizzes and exams to avoid two assessments (tests, quizzes, exams) on the same day.

— Short-format tests matching the student's current concentration span, with the option to test in a quiet environment.

— Clarification: the student does not require extra time to complete tests, but needs each test to be short in duration.

General facilitation:

— Potential provision of human support (AESH: *Accompagnant des Élèves en Situation de Handicap*) to assist with school activities.

— Creation or updating of a Personalized Schooling Plan (PPS) in consultation with the family and the school team.

These measures aim to ensure the continuity of _____'s schooling under the best possible conditions, taking into account specific needs while promoting academic success and well-being.
I remain available to provide the school physician with any additional information or medical documentation needed to evaluate this request.
Pending your response, I thank you in advance for your attention to this situation and for the steps you will take to support my patient.
Please accept my best regards. [1]

1. For insight into what young people with this illness experience, please see: `https://pediatrie.longcovidbelgium.be/`

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